Protocol Number: CA012004
IND Number: 128376
EUDRACT Number 2015-004816-39
Date: 18-Feb-2016
Revised Date: 08-Feb-2019

CLINICAL PROTOCOL CA012004:

A Phase 1/2a Study of BMS-986178 Administered Alone or in Combination with Nivolumab and/or Ipilimumab in Subjects with Advanced Solid Tumors

Revised Protocol Number: 06

Study Director and Medical Monitor
Derrick McKinley, MD

[redacted]

to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 06	08-Feb-2019	To remove retreatment and Survival/Response FU visits for subjects in Part 1-8. To remove certain PK/PD samples
Revised Protocol 05	11-Dec-2017	Incorporates Administrative Letters 04, 05, 06, and 07 and the following: • Addition of Part 8 • Update of Appendix 1 • Update schedule of assessments • Update of address • Typographical errors were corrected, and edits were made for consistency and clarity
Administrative Letter 07	19-Oct-2017	Clarify that if subjects continue for additional cycles, past cycle 4, all study drugs will continue for all cycles in Parts 7A and 7B in Sections 3.1.4.2 and 3.1.5.8 and acknowledge the ommission of the word 'Beyond' in Table 5.1-6
Administrative Letter 06	11-Jul-2017	Correction of typographical errors in Sections 5.1 and 5.5.1
Administrative Letter 05	03-May-2017	Correction of typographical error in Section 3.1.6
Administrative Letter 04	02-May-2017	Correction of typographical error in Section 3.1.6
Revised Protocol 04	04-Apr-2017	Incorporates Amendment 04 and Administrative Letters 02 and 03
Amendment 04	04-Apr-2017	The amendment includes the following: • Addition of Parts 4, 5, 6, and 7 • Update of study title • [redacted] • [redacted] • Update of study design and study visit schematic • Update of inclusion and exclusion criteria to include the new parts and clarify the maximum number of prior treatments allowed • Update of study drug dosing and method of assigning subjects • Update of dose delay language and addition of criteria for resuming treatment in subjects with an infusion reaction • Update/addition of tables for treatment procedures, pharmacokinetic and anti-drug antibody sampling schedule, and pharmacodynamic/ biomarker sampling schedule • Update of sample size information to include the new parts • Update of Appendix 1 to include statistical methods for the new parts • Typographical errors were corrected, and edits were made for consistency and clarity.
Administrative	16-Dec-2016	Change in Study Director/Medical Monitor address

Document	Date of Issue	Summary of Change
Letter 03		
Administrative Letter 02	12-Dec-2016	Correction of typographical error in Section 3.1.3.6, first paragraph, first sentence
Revised Protocol 03	23-Nov-2016	Incorporates Amendment 03 and Administrative Letter 01
Amendment 03	23-Nov-2016	The amendment includes the following: • Removal of Part 1B • Addition of Part 2D, 2E, 3C and Part 2A cohort dose -1 • Change to have imaging as central read • Add text to allow for intermediate and lower doses in escalation • Included text to add potentially more than 1 dose at RP2D • Updated versions numbers for current IB's. • Updating to the new PMD for WOCBP Section • Require fresh tumor biopsy from all subjects • Additional sample to be collected in combination cohorts for RO • Update to not require archived tumor biopsies • Updated Statistical Analysis section • Typographical errors were corrected, and clarifications were made for consistency.
Administrative Letter 01	14-Jun-2016	Correction of typographical error in Section 3.3.1, inclusion criterion 10(g) and Table 5.1-1, Screening Procedure Outline, complete blood count (CBC) with differential
Revised Protocol 02	08-Jun-2016	Incorporates Amendment 02
Amendment 02	08-Jun-2016	The purpose of this amendment is to address comments received from Health Authorities. The amendment includes the following: • Change the definition for "Related AE's" and "Not Related AE's". • Update prior therapy inclusion criteria for dose escalation subjects. • Remove timeframe from hematologic DLT grade 3 febrile neutropenia. • Change to have CBC with differential processed through LLDS. • Add new model document language for Additional Research Collection and Imaging scans. • Typographical errors were corrected, and clarifications were made for consistency.
Revised Protocol 01	26-Apr-2016	Incorporates Amendment 01
Amendment 01	26-Apr-2016	The purpose of this amendment is to address comments received from Health Authorities. The amendment includes the following: • The timing of the initiation of combination therapy dose escalation cohorts was revised, a sentinel subject was added to all dose cohorts, Parts 1B and 2B were removed and the subsequent study parts were renamed (Part 1C to Part 1B, Part 2C to Part 2B, and Part 2D to Part

Document	Date of Issue	Summary of Change
		2C), DLT period across the study (28 days) was made uniform, the post-infusion observation period was extended to 4 hours, contraceptive requirements were updated, lipase and amylase ≤ 1.5×ULN were removed as criteria for adequate organ function, DLT criteria were revised, a timepoint was added for safety monitoring, the rationale for use of blood and tumor tissue in biomarker studies was clarified, prior therapy requirements for dose expansion cohorts were updated, and BLRM language was clarified. • Typographical errors were corrected, and clarifications were made for consistency.
Original Protocol	18-Feb-2016	Not applicable

[redacted]

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	[redacted]
3.1.6, Study Schedule	Deleted references to Response Follow-up and Survival Follow-up periods.	
Figure 3.1.6-1: Study Visit Schematic	Deleted references to Response Follow-up and Survival Follow-up periods as well as to retreatment options for all parts.	
3.1.6.4, Survival Follow-up	Deleted entire section.	
3.1.6.5, Response Follow-up	Deleted entire section.	
3.1.7, Treatment with Additional Cycles	Deleted reference to retreatment options.	
3.1.9, Retreatment during Response Follow-Up	Deleted entire section.	
3.4.1. Prohibited and/or Restricted Treatments	Deleted reference to the survival follow-up period.	
3.5.1.2, Assessment Schedule for Subjects with Post-progression Treatment	Deleted reference to Retreatment Table 5.1-9.	
3.6, Post-study Drug Follow-up	Deleted references to Response Follow-up and Survival Follow-up periods.	
4.5.5.1, Criteria to resume treatment in subjects with a dose delay.	Clarified bullet regarding resumption of treatment after grade 1 pneumonitis.	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06

Section Number & Title	Description of Change	[redacted]
5.1, Flow Chart/Time and Events Schedule Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, Table 5.1-6, Table 5.1-7, Table 5.1-8, Table 5.1-9.	Deleted reference to retreatment, including references to retreatment PK and Biomarker tables (Table 5.5.1-3, Table 5.5.1-5, Table 5.5.1-7, Table 5.5.1-9, and Table 5.6-6) in Table 5.1-2 through Table 5.1-8. Deleted Retreatment Table 5.1-9.	
5.3, Safety Assessments	Deleted reference to Retreatment Table 5.1-9.	
5.3.2, Laboratory Test Assessments	Deleted reference to retreatment period.	
5.4, Efficacy Assessments	Added part of sentence: “then every 12 weeks during the Response Follow-up phases (for subjects who already have data collected)”, to keep consistency with Synopsis.	
5.5, Pharmacokinetic Assessments	Deleted references to retreatment PK tables (Table 5.5.1-3, Table 5.5.1-5, Table 5.5.1-7, and Table 5.5.1-9).	
5.5.1, Pharmacokinetics and Immunogenicity Collection and Processing	Deleted references to retreatment PK tables (Table 5.5.1-3, Table 5.5.1-5, Table 5.5.1-7, and Table 5.5.1-9).	
Table 5.5.1-1, Table 5.5.1-2, Table 5.5.1-4, Table 5.5.1-6, Table 5.5.1-8, and Table 5.5.1-10	Deleted all assessments beginning with Cycle 5 including follow-up assessment (retained EOT assessments).	
Table 5.5.1-3, Table 5.5.1-5, Table 5.5.1-7, and Table 5.5.1-9	Deleted entire retreatment tables.	
5.6, Biomarker Assessments	Deleted reference to retreatment, Biomarker table (Table 5.6-6).	
Table 5.6-1, Table 5.6-2, and Table 5.6-3	Deleted all assessments beginning with Cycle 5 (retained EOT assessments).	
Table 5.6-6	Deleted entire retreatment table.	
5.7.1.2, Whole Blood Gene Expression	Deleted reference to retreatment, Biomarker table (Table 5.6-6).	
5.7.1.3, Whole Blood Immune Assay	Deleted reference to retreatment, Biomarker table (Table 5.6-6).	
5.7.1.4, Serum and Plasma Factors	Deleted reference to retreatment, Biomarker table (Table 5.6-6).	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	[redacted]
5.7.2.1, Tissue Biopsies from All Subjects	Deleted reference to retreatment, Biomarker table (Table 5.6-6).	
8.3.2.1, Efficacy	Added part of sentence: "then every 12 weeks during the Response Follow-up phases (for subjects who already have data collected)", to keep consistency with Synopsis.	

SYNOPSIS

Clinical Protocol CA012004

Protocol Title: A Phase 1/2a Study of BMS-986178 Administered Alone or in Combination with Nivolumab and/or Ipilimumab in Subjects with Advanced Solid Tumors

Investigational Product(s), Dose and Mode of Administration, and Duration of Treatment with Investigational Product(s):

BMS-986178, an anti-OX40 agonist monoclonal antibody (mAb) supplied as a sterile 25-mg/mL formulation, is to be administered as an intravenous (IV) infusion alone or in combination with nivolumab and/or ipilimumab per the cohort assignment and the duration of treatment, as indicated in the protocol. Nivolumab, an anti-programmed cell death-1 (PD-1) mAb, is available as a sterile 10-mg/mL formulation to be administered as an IV infusion. Ipilimumab, an anti-cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) mAb, is available as a sterile 5-mg/mL formulation to be administered as an IV infusion.

Study Phase: 1/2a

Research Hypothesis: It is anticipated that anti-OX40 agonist antibody (BMS-986178), administered as a single agent or in combination with anti-PD-1 mAb (nivolumab) or anti-CTLA-4 mAb (ipilimumab), will demonstrate adequate safety and tolerability, as well as a favorable risk/benefit profile, to support further clinical testing. No prospective hypotheses are being formally evaluated.

Objectives:

Primary Objective:

The primary objective is to determine the safety, tolerability, dose-limiting toxicities (DLTs), and maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab in subjects with advanced solid tumors.

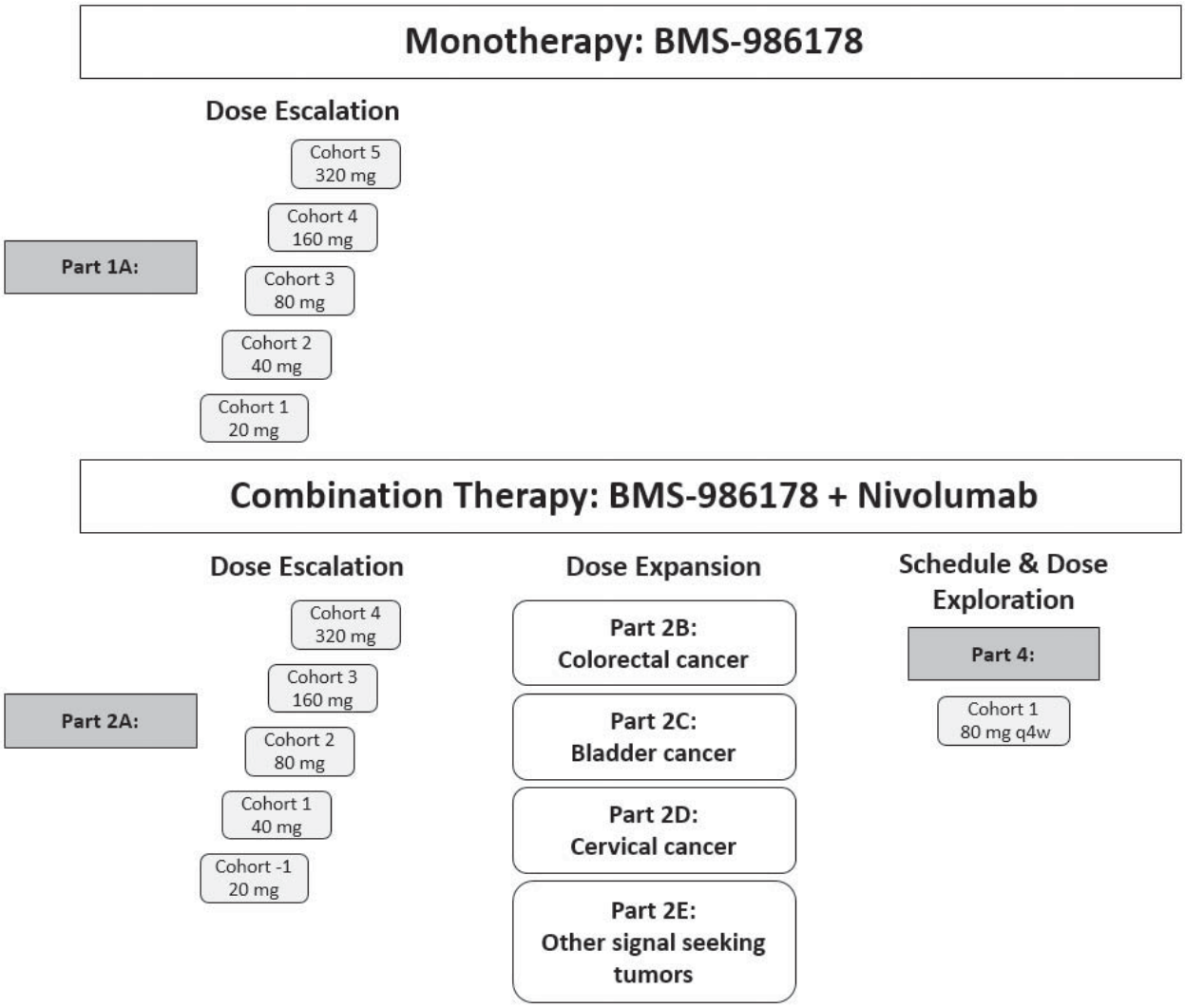
Secondary Objectives:

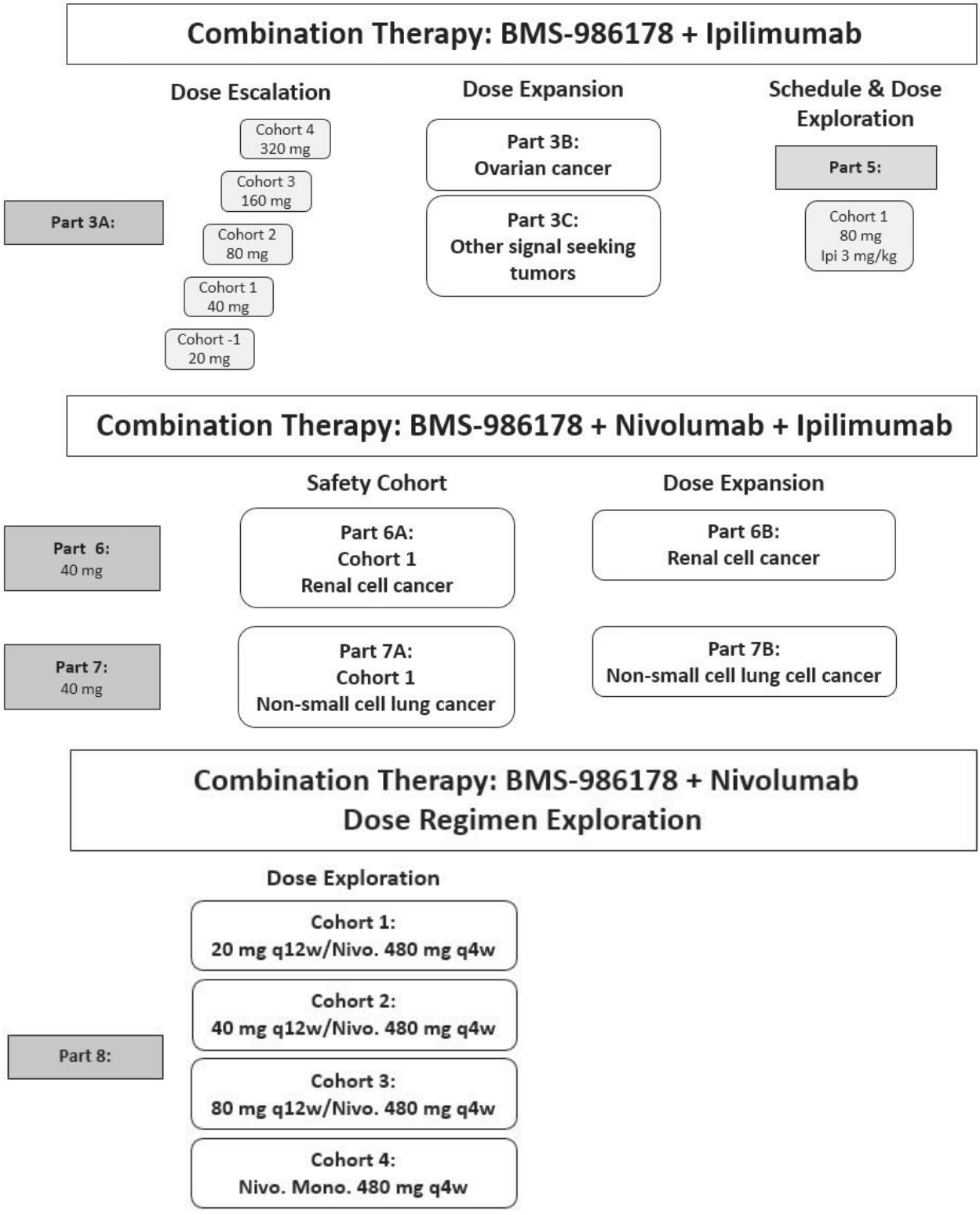
- To investigate the preliminary anti-tumor activity of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab in subjects with advanced solid tumors
- To characterize the pharmacokinetics (PK) of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab
- To characterize the immunogenicity of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab and the immunogenicity of nivolumab or ipilimumab administered with BMS-986178
- To assess the proportion of subjects showing a change in peripheral pharmacodynamic biomarkers such as soluble OX40 and peripheral OX40 receptor occupancy along with tumor pharmacodynamic of BMS-986178 in combination with nivolumab or nivolumab monotherapy (Part 8)

Study Design:

This is a Phase 1/2a, open-label study of BMS-986178 in subjects with advanced solid tumors that integrates initial BMS-986178 monotherapy with subsequent nivolumab and/or ipilimumab combination therapy. Study sections (dose escalation and dose expansion) will proceed in a phased approach that is based upon study-emergent safety, PK, and PD data. The first section of the study will begin with BMS-986178 monotherapy dose escalation cohorts. The clinical data from the first 3 monotherapy dose cohorts will serve as a foundation for initiating dose escalation of BMS-986178 in combination with nivolumab. The clinical data from the first 3 monotherapy dose cohorts in addition to the clinical data from the first cohort of BMS-986178 in combination with nivolumab will then serve as a foundation for initiating dose escalation of BMS-986178 in combination with ipilimumab. The clinical data for BMS-986178 in combination with nivolumab and BMS-986178 in combination with ipilimumab will serve as the foundation for initiating combination therapy of BMS-986178 with nivolumab and ipilimumab in Parts 6 and 7. After establishment of a tolerable and pharmacologically active MTD/RP2D of BMS 986178 in the dose escalation and schedule and dose exploration sections, dose expansion in specific tumor cohorts will be initiated. Recent preclinical and clinical data will serve as the foundation for focusing on further optimizing the dose of BMS-986178 in combination with nivolumab.

Figure -1: Study Design Schematic (Parts 1 to 8)





Dose levels are specific for each part. Dose expansion will begin only after MTD/RP2D determination in the corresponding dose escalation phases of the study.

Abbreviations: MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose.

Summary of Study Design:

Dose Escalation (Parts 1A, 2A, and 3A):

The dose escalation part of the study will evaluate the safety and tolerability of BMS-986178 alone or in combination with nivolumab or ipilimumab in subjects with advanced solid tumors.

The initial dose level of BMS-986178 planned for this study is 20 mg. Dose escalation decisions for subsequent doses will be based on DLTs using a Bayesian Logistic Regression Method (BLRM; for BMS-986178 monotherapy) or a BLRM (-Copula) model (for BMS-986178 in combination with nivolumab and/or ipilimumab). The DLT period is 28 days for both monotherapy and combination therapy dose escalation parts. The DLT rate will be determined based on the incidence, severity, and duration of AEs that occur within the DLT period and for which no alternative cause can be identified. Dose selection for the next monotherapy cohort/dose level will take into account the BLRM (-Copula) recommendation in conjunction with the clinical recommendation and all available PK, PD, immunogenicity, and clinical and laboratory safety data from all treated subjects. Starting dose selection of BMS-986178 for Part 2A will be determined using data available from Part 1A, including clinical and laboratory safety assessments, PK/PD data, immunogenicity, and modeling recommendation within Bayesian modeling framework by incorporating single-agent toxicity profiles of both BMS-986178 (Part 1A) and nivolumab (CA209-003). Starting dose selection of BMS-986178 for Part 3A will be determined using data available from Parts 1A and 2A, including clinical and laboratory safety assessments, PK/PD data, and modeling recommendation within Bayesian modeling framework by incorporating single-agent toxicity profiles of both BMS-986178 (Part 1A) and ipilimumab (CA184-022). The final dose escalation decision will be made after discussion and agreement between the investigators and the BMS Medical Monitor. Actual doses can be modified per the BLRM (-Copula) but will not exceed doubling of the previously tested doses. Escalation by more than 1 dose level (dose skipping) is not permitted.

During dose escalation for all dose cohorts, the initial subject (sentinel subject) will be observed for 5 days before additional subjects in that cohort are treated with study drug.

Approximately 30 subjects will be enrolled in each dose escalation part. The number of subjects in each dose escalation cohort may vary depending on the BLRM (-Copula) recommendations. Initially, approximately 3 subjects will be treated at the starting dose levels of BMS-986178 or BMS-986178 in combination with nivolumab or ipilimumab. Additional cohorts of approximately 3 evaluable subjects will be treated at recommended dose levels per BLRM (-Copula) during the dose escalation phase. At least 6 DLT-evaluable subjects will be treated at the MTD.

Part 1A: Enrollment will begin in Part 1A, BMS-986178 monotherapy dose escalation. The initial dose of BMS-986178 for Part 1A will be 20 mg with expected subsequent doses of 40, 80, 160, and 320 mg. Actual doses can be modified per the BLRM but will not exceed doubling of the previously tested dose.

Parts 2A and 3A: Part 2A is the combination arm of BMS-986178 with nivolumab that will be initiated only after **at least** 3 dose levels in the monotherapy dose escalation have been found to be tolerated or an MTD/RP2D has been determined in the monotherapy dose escalation (Part 1A). The starting dose of BMS-986178 in Part 2A will be at least 1 dose level below a dose that was demonstrated to be tolerated in Part 1A, and at no time will the dose for BMS-986178 in Part 2A exceed the highest tolerated dose in Part 1A. To ensure further safety of the combination. Part 3A is the combination arm of BMS-986178 with ipilimumab that will be initiated only after at least 3 dose levels in the monotherapy dose escalation have been found to be tolerated or an MTD/RP2D has been determined in the monotherapy dose escalation (Part 1A) **and** at least 1 dose cohort has been found to be tolerated in the BMS-986178 with nivolumab dose escalation part (Part 2A). The starting dose of BMS-986178 in Part 3A will be at least 1 dose level below a dose that was demonstrated to be tolerated in Part 1A, and at no time will the dose for BMS-986178 in Part 3A exceed the highest tolerated dose in Part 1A to further ensure safety of the combination doses in treated subjects. In Parts 2A and 3A, doses intermediate to previously tested doses or doses lower than the starting dose may be explored to further characterize the dose response for safety, PK, or PD as appropriate based on clinical data collected.

Schedule and Dose Exploration (Parts 4, 5, and 8):

Part 4: Part 4 is the combination arm of BMS-986178 with nivolumab (480 mg) to be administered every 4 weeks (q4w). The dose of BMS-986178 will be a dose previously evaluated in Part 2A that has been found to have a manageable safety profile and at no time will the dose for BMS-986178 exceed the highest tolerated dose in Part 2A, in which every 2 weeks (q2w) dosing is explored. Approximately 6 to 12 subjects will be treated in this cohort.

Part 5: Part 5 is the combination arm of BMS-986178 with ipilimumab (3 mg/kg) to be administered every 3 weeks (q3w) for 4 doses, followed by monotherapy with BMS-986178 (maintenance therapy). The dose of BMS-986178 will be a dose previously evaluated in Part 3A that has been found to have a manageable safety profile and at no time will the dose for BMS-986178 exceed the highest tolerated dose in Part 3A. Approximately 6 to 12 subjects will be treated in this cohort.

Part 8: Part 8 is the dose regimen exploration arm of BMS-986178 with a less frequent dosing schedule at either 20 mg, 40 mg, and 80 mg q12w in combination with nivolumab flat dose (480 mg; q4w) dose level (Cohort 1-3) or nivolumab 480 mg flat dose q4w monotherapy (Cohort 4) A tetanus vaccine (Tdap preferred, Td or equivalent after discussion with the medical monitor) will be administered to all subjects on Cycle 1 Day 1. Approximately 20 subjects will be treated in each cohort. Administration of a recall antigen such as tetanus toxoid may provide potent recall response with BMS-986178 in combination with nivolumab or nivolumab monotherapy.

Safety Cohorts (Parts 6A and 7A):

Part 6A: Part 6A is the safety cohort for combination of BMS-986178 with ipilimumab and nivolumab in subjects with renal cell carcinoma (RCC). BMS-986178 will be administered at a flat dose of 40 mg in combination with nivolumab (240 mg) and ipilimumab (1 mg/kg) q3w during Cycles 1 to 4 followed by maintenance therapy in which BMS-986178 (40 mg) and nivolumab (480 mg) will be administered q4w.

Part 7A: Part 7A is the safety cohort for combination of BMS-986178 with ipilimumab and nivolumab in subjects with non-small cell lung cancer (NSCLC). BMS-986178 will be administered at a flat dose of 40 mg (q2w) in combination with nivolumab (240 mg; q2w) and ipilimumab (1 mg/kg; q6w) for four 6-week cycles.

Dose Expansion (Parts 2B, 2C, 2D, 2E, 3B, 3C, 6B, and 7B):

Treatment in the dose expansion cohorts will be initiated when the MTD/RP2D has been determined based on the evaluation of totality of available clinical safety (DLTs, AEs occurring after the DLT period), PK, PD, immunogenicity, and modeling data from the dose escalation parts (1A, 2A, and 3A) or schedule and dose exploration parts (4 and 5). Approximately 294 subjects will be treated in all dose expansion cohorts.

Parts 2B, 2C, 2D, and 2E (combination with nivolumab) are the dose expansion parts in subjects with colorectal cancer, bladder cancer, cervical cancer, and other tumors from dose escalation for signal finding, respectively, at the MTD/RP2D(s) determined in Parts 2A or 4.

Part 3B (combination with ipilimumab) is the dose expansion part in subjects with ovarian cancer at the MTD/RP2D(s) determined in Parts 3A or 5. Part 3C (combination with ipilimumab) is the dose expansion part in subjects with other tumors from dose escalation for signal finding at the MTD/RP2D(s) determined in Part 3A or 5.

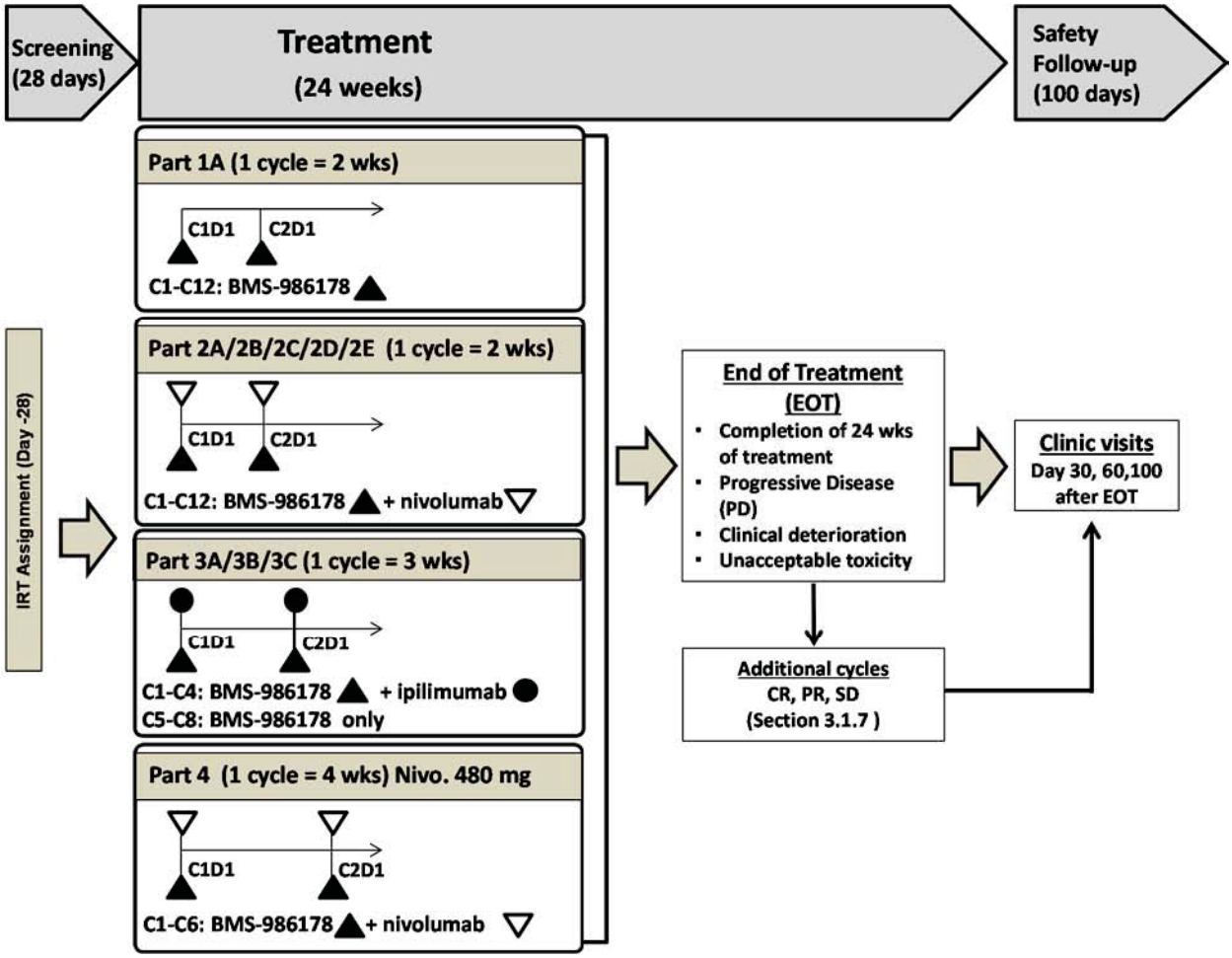
Part 6B (combination with nivolumab and ipilimumab) is the dose expansion part in subjects with RCC at a tolerable dose determined in Part 6A.

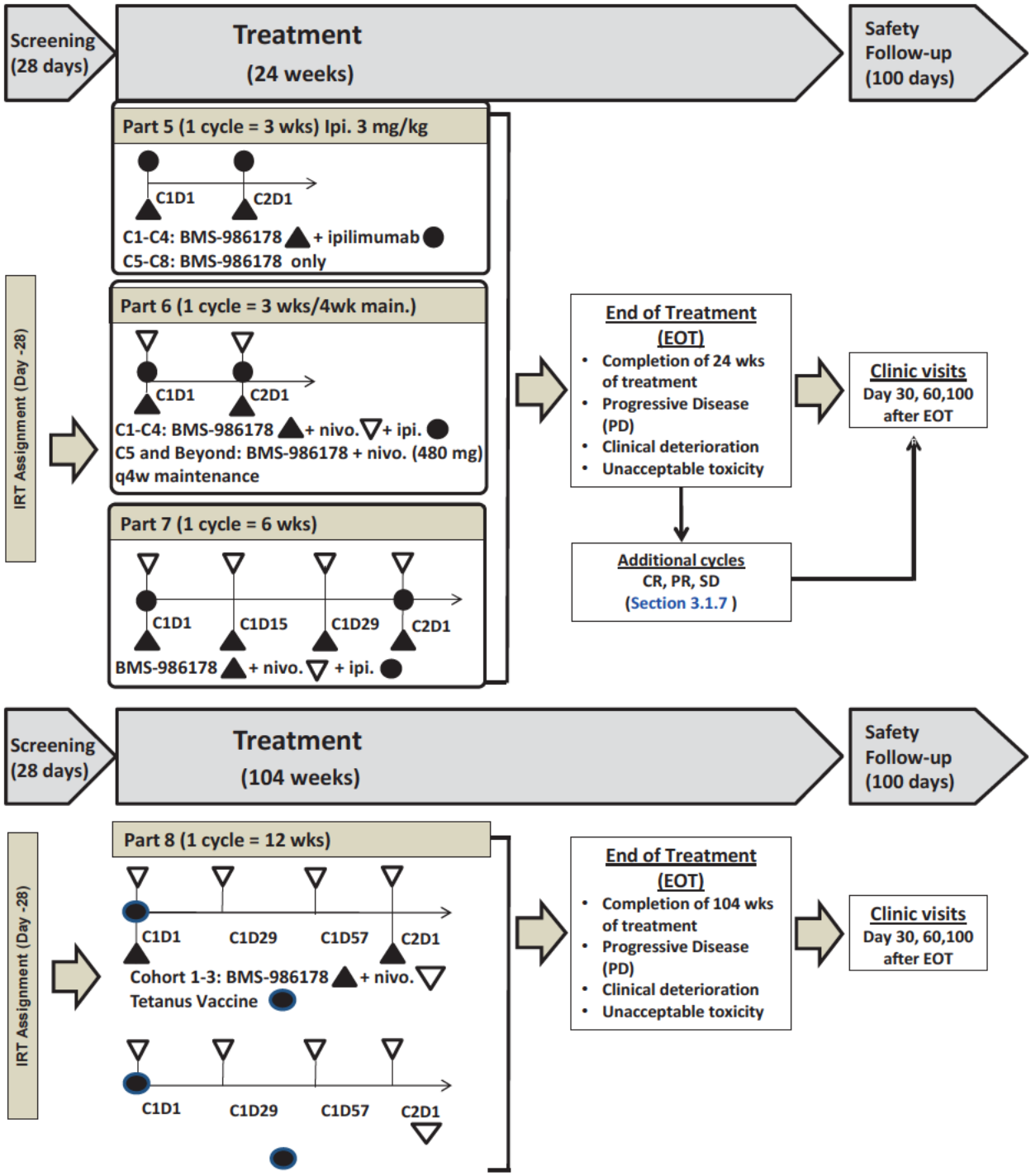
Part 7B (combination with nivolumab and ipilimumab) is the dose expansion part in subjects with NSCLC at a tolerable dose determined in Part 7A.

Summary of Study Periods:

Subjects will complete: Screening (up to 28 days), Treatment (up to 24 weeks of dosing for Part 1-7, up to 24 months of dosing for Part 8, or until meeting protocol-specified discontinuation criteria) and Safety Follow-up of approximately 100 days. As of Protocol Revision 06, no new subjects will enter the Response Follow-up or Survival Follow-up period. For Part 8 subjects and any subjects in Part 2, 4, 6, or 7 that have approval for additional cycles up to 2 years of treatment. The study visit schematic is presented in Figure -2.

Figure -2: **Study Visit Schematic**





Abbreviations: CR = complete response; EOT = end of treatment; FU = Follow-up; Ipi = ipilimumab; IRT = Interactive Response Technology; Nivo = nivolumab; PR = partial response; SD = stable disease; wks = weeks.

Screening Period:

The Screening period will last for up to 28 days. The screening period begins by establishing the subject's initial eligibility and signing of the informed consent form. Subjects will be enrolled using an Interactive Response Technology (IRT).

Treatment Period:

The Treatment period consists of up to 24 weeks of dosing for Part 1-7. Part 8 will have a treatment period for up to 24 months of dosing. Following each treatment cycle, the decision to treat a subject with the next cycle of study therapy, up to 24 weeks of treatment or Part 8 up to 24 months, will be based on risk/benefit and tumor assessments. Tumor assessments will be performed every 8 weeks for Part 1-7 or every 12 weeks for Part 8 (± 1 week). Assessments of partial response (PR) and complete response (CR) must be confirmed at least 4 weeks following initial assessment. Tumor progression or response endpoints will be assessed using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1.

Subjects with a response of stable disease (SD), PR, or CR at the end of a given cycle will continue to the next treatment cycle. Subjects will generally be allowed to continue study therapy until the first occurrence of one of the following: 1) completion of the maximum number of cycles; 2) progressive disease; 3) clinical deterioration suggesting that no further benefit from treatment is likely; 4) intolerability to therapy; or 5) meeting the criteria for discontinuation of study therapy as outlined in the protocol.

Safety Follow-up:

Upon completion of study therapy, subjects will enter the Safety Follow-up period. After the end of treatment (EOT) visit, subjects will be evaluated for any new adverse events (AEs) for approximately 100 days after the last dose of therapy. Follow-up visits should occur at Days 30, 60 and 100 after the last dose or the date of discontinuation. Subjects (except those who withdraw consent for study participation) are expected to complete the 3 clinical Safety Follow-up visits regardless of whether they start new anti-cancer therapy.

Duration of Study: The total duration of study time for any individual subject is expected to be approximately 2.5 years (depending on Part subject is randomized to). The study will end when the last subject completes their last study visit, which is planned to be about 4 years after the start of the study.

Number of Subjects: Approximately 604 subjects will be enrolled, and approximately 515 subjects will be treated in the study.

Study Population: Subjects must be at least 18 years old and have histologic or cytologic confirmation of a malignancy that is advanced (metastatic, recurrent, refractory and/or unresectable) with measurable disease per RECIST v1.1.

Study Drug: Investigational products are as listed in Table -1.

Table -1: Study Drugs for CA012004

Product Description Class and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per label)
BMS-986178 Injection	25 mg/mL (80 mg/vial)	IP	Open	Colorless to pale yellow liquid. Clear to slightly opalescent. Light (few) particulates (consistent in appearance to proteinaceous particulates) may be present.	Store at 2°C to 8°C; do not freeze; protected from light.
Nivolumab Injection	10 mg/mL (100 mg/vial)	IP	Open	Clear to opalescent, colorless to pale yellow liquid. Light (few) particulates may be present.	Store at 2°C to 8°C; store in original package; do not freeze;

Table -1: Study Drugs for CA012004

Product Description Class and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per label)
					protected from light.
Ipilimumab Injection	5 mg/mL (200 mg/vial)	IP	Open	Clear, colorless liquid. Light (few) particulates may be present.	Store at 2°C to 8°C; do not freeze; protected from light.
Tetanus vaccine	Per local[a]	IP	Open	Various packaging configuration	Refer to the label on container and/or pharmacy manual

Abbreviation: IP = investigational product

[a] Tetanus vaccine (Tdap preferred, Td or equivalent after discussion with the medical monitor)will be obtained as local commercial product in countries if allowed by local regulations or through investigating sites standard prescribing procedures.

Study Assessments:

- Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Subjects will be closely monitored for AEs throughout the study.
- Safety Assessments: AEs will be assessed during the study and for 100 days after the last treatment. AEs will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities and reviewed for potential significance and importance. Subjects will be followed until all treatment-related AEs have recovered to baseline or are deemed irreversible by the investigator.
- Efficacy Assessments: Disease assessment with computed tomography and/or magnetic resonance imaging as appropriate will be performed at baseline and every 8 weeks (± 1 week) per RECIST v1.1 until discontinuation of treatment or withdrawal from study. Tumor assessments at other time points may be performed if the investigator is concerned about tumor progression. Assessment of tumor response will be reported by the investigator as defined by RECIST v1.1 for subjects with advanced solid tumors.
- Pharmacokinetic and Immunogenicity Assessments: Samples for PK and immunogenicity assessments will be collected for subjects receiving BMS-986178 alone or in combination with nivolumab and/or ipilimumab. The PK of BMS-986178 will be characterized by non-compartmental analysis method. Immunogenicity samples will be analyzed for anti-BMS-986178 antibodies and/or anti-nivolumab antibodies and/or anti-ipilimumab antibodies by validated immunoassays.

[redacted]

Statistical Considerations:

Sample Size Determination:

Dose Escalation (Parts 1A, 2A, and 3A):

As a Phase 1 dose escalation trial, the sample size for each dose escalation cohort depends on observed toxicity and posterior inference. Approximately 30 subjects are expected to be treated during each dose escalation part (BMS-986178 monotherapy [Part 1A], BMS-986178 in combination with nivolumab [Part 2A], and BMS-986178 in combination with ipilimumab [Part 3A]) for a combined total of approximately 90 subjects in Parts 1A, 2A and 3A. Initially, approximately 3 subjects will be treated at the starting dose levels of BMS-986178 or BMS-986178 in combination with nivolumab or ipilimumab. Additional cohorts of approximately 3 evaluable subjects will be treated at recommended dose levels per BLRM (-Copula) recommendations during the dose escalation phase. At least 6 DLT-evaluable subjects will be treated at the MTD.

Schedule and Dose Exploration (Parts 4, 5, and 8):

Approximately 6 to 12 subjects are expected to be treated during each schedule and dose exploration part (BMS-986178 in combination with nivolumab [Part 4] and BMS-986178 in combination with ipilimumab [Part 5] for a combined total of approximately 12 to 24 subjects in Parts 4 and 5).

Approximately 20 evaluable subjects per dose cohort will be treated in Part 8 of the study, BMS-986178 in combination with nivolumab (Cohort 1-3) and monotherapy nivolumab (Cohort 4). Total number of subjects in this Part 8 will be approximately 80.

Safety Cohorts (Parts 6A and 7A):

Approximately 6 to 12 subjects are expected to be treated during each safety cohort part (BMS-986178 in combination with nivolumab and ipilimumab q3w, followed by maintenance therapy with combination of BMS-986178 and nivolumab q4w [Part 6A], and BMS-986178 in combination with nivolumab [q2w] and ipilimumab [q6w; Part 7A]), for a combined total of approximately 12 to 24 subjects in Parts 6A and 7A.

Cohort Expansion (Parts 2B, 2C, 2D, 2E, 3B, 3C, 6B, and 7B):

In general terms, the expansion phase sizing is guided by Simon 2-stage design, which is based on target response rates (target overall response rate) and the ability to identify a signal for such clinical response that is above the standard of care (historical overall response rate). It is not the intent of this study to use Simon 2-stage design for formal hypothesis testing.

Disease-restricted population cohorts will be guided by the Simon 2-stage design. Approximately 35 subjects will be treated in the Part 2B dose expansion cohort. Approximately 27 subjects will be treated in the Part 2C dose expansion cohort. Approximately 37 subjects will be treated in the Part 2D dose expansion cohort. Approximately 35 subjects will be treated in the Part 3B dose expansion cohort. Approximately 40 subjects will be treated in each Parts 2E and 3C of dose expansion portion will include other tumors from dose escalation for signal seeking. Due to the heterogeneity of response rates of the mixed tumors, Simon 2-stage design is not pursued for Parts 2E and 3C. Approximately 40 subjects each will be treated in dose expansion Parts 6B and 7B. Additional subjects may be treated in order to have sufficient response-evaluable subjects per expansion cohort.

Endpoints:

Primary Endpoints:

The assessment of safety will be based on the incidence of AEs, serious AEs, AEs leading to discontinuation, and deaths. In addition, clinical laboratory test abnormalities will be examined.

Secondary Endpoints:

Efficacy: The anti-tumor activity of BMS-986178 alone or in combination with nivolumab and/or ipilimumab will be measured by ORR, duration of response, and progression free survival rate (PFSR) at 24 weeks based on RECIST v1.1. The above will be determined based on tumor measurements occurring at baseline, every 8 weeks (± 1 week) during the treatment period, and every 12 weeks during the Response Follow-up phases (for subjects who already have data collected).

- Best overall response (BOR) is assessed by investigator and/or BICR per RECIST 1.1 criteria.
- ORR is defined as the proportion of all treated subjects whose BOR is either CR or PR.
- Duration of response, computed for all treated subjects with a BOR of CR or PR, is defined as the time between the date of first response and the date of disease progression or death, whichever occurs first.
- PFSR at 24 weeks is defined as the proportion of treated subjects remaining progression-free and surviving at 24 weeks. The proportion will be calculated by the Kaplan-Meier estimate, which takes into account censored data.

Pharmacokinetics: Selected BMS-986178 parameters, such as Cmax, Tmax, AUC(0-t), and AUC(TAU), will be assessed in 2 cycles depending on the schedule for monotherapy or in combination with nivolumab and/or ipilimumab. Parameters such as Ctau, CLT, Css-avg, accumulation index (AI), and effective elimination half-life (T-HALFeff) will be assessed in the second cycle when intensive PK are collected. A separate listing, summary, and plot will be generated for Ctrough.

Immunogenicity: The secondary objective of immunogenicity will be assessed by the frequency of positive ADA to BMS-986178 or nivolumab or ipilimumab.

Pharmacodynamics: The secondary objective of pharmacodynamics will be assessed by the proportion of subjects showing a change in pharmacodynamic biomarkers such as soluble OX40 and peripheral OX40 receptor occupancy along with tumor pharmacodynamic of BMS-986178 in combination with nivolumab or nivolumab monotherapy (Part 8).

[redacted]

Analyses:

Safety analyses: All recorded AEs will be listed and tabulated by system organ class, preferred term, and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator, and abnormalities, if present, will be listed.

Efficacy analyses: The primary efficacy analyses will be performed on all treated subjects. Efficacy analyses based on response-evaluable subjects may be performed for interim analyses when the minimum follow up period is less than sufficient to warrant adequate interpretation of results. Listing of tumor measurements will be provided by subject and study day in each arm and dose level. Individual subject's BOR will be listed based on RECIST 1.1.

To describe the anti-tumor activity of BMS-986178 alone or in combination with nivolumab and/or ipilimumab, ORR will be calculated. ORR and corresponding 2-sided 95% CI by the Clopper-Pearson method will be provided by treatment and/or dose level and tumor type. Median duration of response and corresponding 2-sided 95% CI will be reported by treatment and/or dose level and tumor type. Duration of response will be analyzed using the Kaplan-Meier method.

In addition, PFSR, the probability of a subject remaining progression-free or surviving to 24 weeks, will be estimated by the Kaplan-Meier methodology by treatment, tumor type, and dose level. The corresponding 95% CI will be derived based on Greenwood formula.

[redacted]

Pharmacokinetic analyses: All individual PK parameters will be listed for each analyte, including any exclusions and reasons for exclusion from summaries. Summary statistics will be tabulated for each PK parameter by treatment. Geometric means and coefficients of variation will be presented for Cmax, AUC(0-t), AUC(TAU), Ctau, CLT, Css-avg, and AI. Medians and ranges will be presented for Tmax. Means and standard deviations will be presented for all other PK parameters (eg, T-HALFeff).

BMS-986178 dose dependency will be assessed in dose escalation monotherapy. To describe the dependency on dose of BMS-986178, scatter plots of Cmax, AUC(0-t), and AUC(TAU) versus dose may be provided for each day measured. An exploratory assessment of dose proportionality based on a power model and a CI around the power coefficient may be performed. Nivolumab and ipilimumab end of infusion and trough (Ctrough) concentrations and BMS-986178 trough concentration will be tabulated by treatment and study day using summary statistics. These data may also be pooled with other datasets for population PK analysis, which will be presented in a separate report.

Immunogenicity analysis: A listing of all available immunogenicity data will be provided by treatment, dose, and immunogenicity status. The frequency of subjects with positive ADA assessment of BMS-986178, nivolumab, and ipilimumab will be summarized.

Biomarker analyses: In Part 8, summary statistics for the proportion of subjects showing a change in pharmacodynamic biomarkers will be tabulated by treatment cohort.

[redacted]

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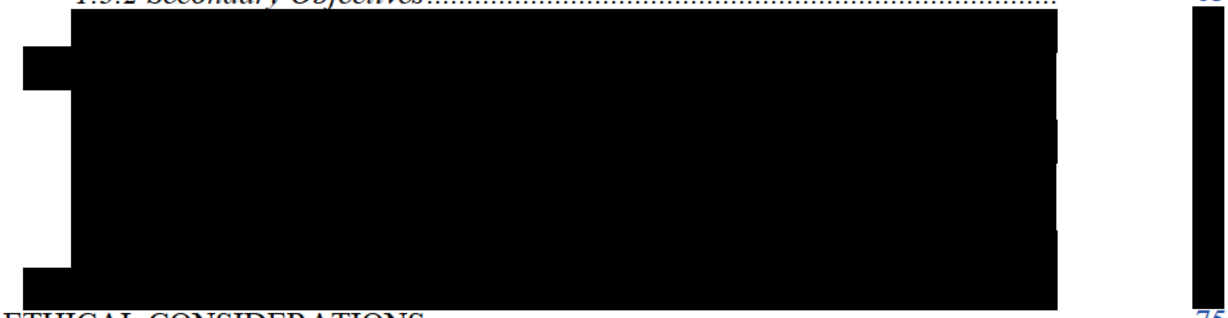

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1.2 Research Hypothesis

It is anticipated that anti-OX40 agonist antibody (BMS-986178), administered as a single agent or in combination with anti-PD-1 antibody (nivolumab) or anti-CTLA-4 (ipilimumab), will demonstrate adequate safety and tolerability, as well as a favorable risk/benefit profile, to support further clinical testing. No prospective hypotheses are being formally evaluated.

1.3 Objectives(s))

1.3.1 Primary Objective

The primary objective is to determine the safety, tolerability, DLTs, and MTD/RP2D of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab in subjects with advanced solid tumors.

1.3.2 Secondary Objectives

- To investigate the preliminary anti-tumor activity of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab, in subjects with advanced solid tumors
- To characterize the PK of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab
- To characterize the immunogenicity of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab, and the immunogenicity of nivolumab or ipilimumab administered with BMS-986178
- To assess the proportion of subjects showing a change in peripheral pharmacodynamic biomarkers such as soluble OX40 and peripheral OX40 receptor occupancy along with tumor pharmacodynamic of BMS-986178 in combination with nivolumab or nivolumab monotherapy (Part 8)

[redacted]

[redacted]

[redacted]

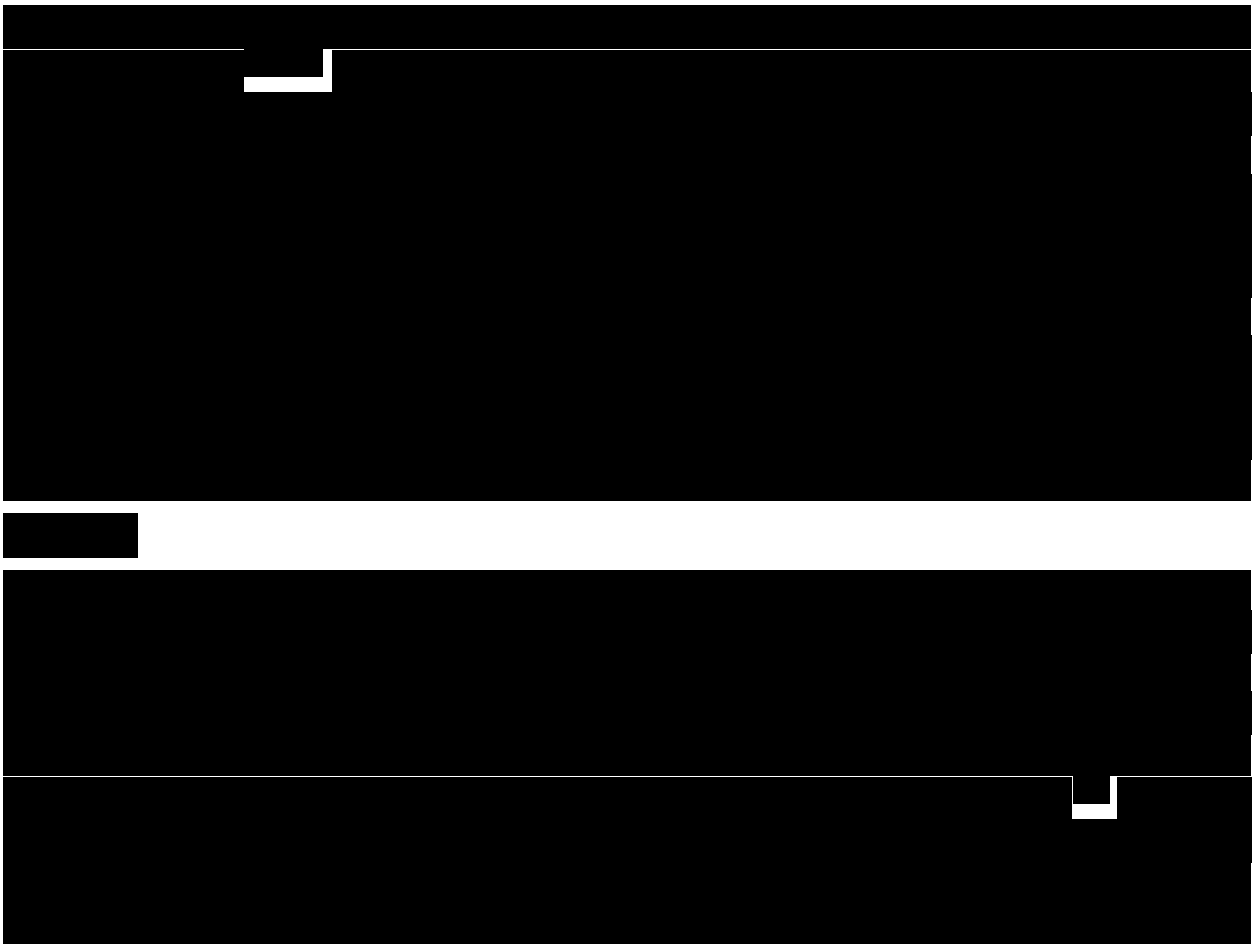
In a 1-month intermittent repeat-dose exploratory study in cynomolgus monkeys (Section 1.4.2), [redacted]

[redacted]

highest tolerated dose in the monotherapy dose escalation arm (Part 1A). The initial subject will

[redacted]

agents results in a safety profile with similar types of AEs to either agent alone, but in some cases,



2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the ICH and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the IB or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form(s) which will include all elements required by ICH, GCP, and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form(s) and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
- If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form(s) must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

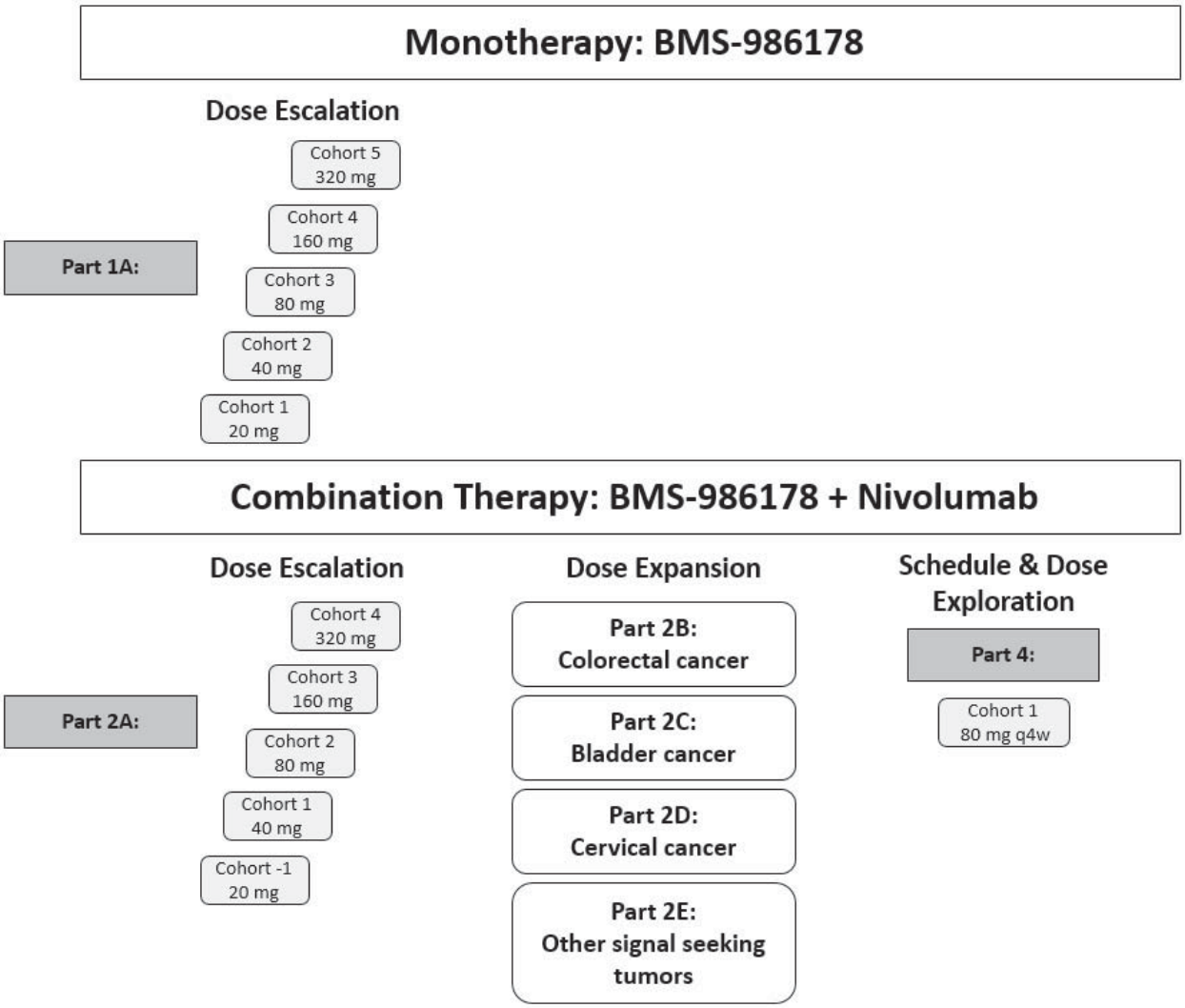
The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

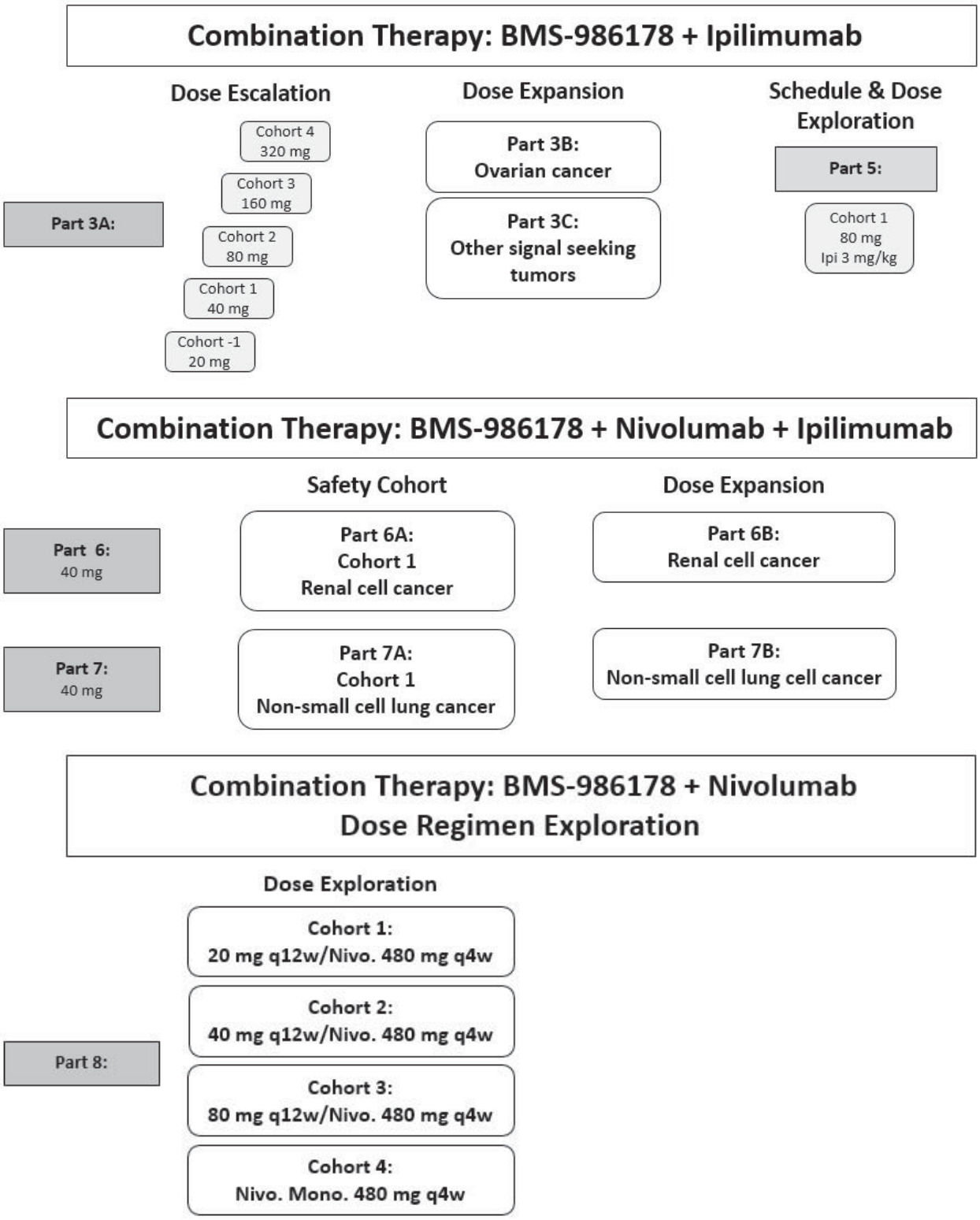
3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a Phase 1/2a, open-label study of BMS-986178 in subjects with advanced solid tumors that integrates initial BMS-986178 monotherapy with subsequent nivolumab and/or ipilimumab combination therapy. Study sections (dose escalation and dose expansion) will proceed in a phased approach that is based upon study-emergent safety, PK, and PD data. The first section of the study will begin with BMS-986178 monotherapy dose escalation cohorts. The clinical data from the first 3 monotherapy dose cohorts will serve as a foundation for initiating dose escalation of BMS-986178 in combination with nivolumab. The clinical data from the first 3 monotherapy dose cohorts in addition to the clinical data from the first cohort of BMS-986178 in combination with nivolumab will then serve as a foundation for initiating dose escalation of BMS-986178 in combination with ipilimumab. The clinical data for BMS-986178 in combination with nivolumab and BMS-986178 in combination with ipilimumab will serve as the foundation for initiating combination therapy of BMS-986178 with nivolumab and ipilimumab in Parts 6 and 7. After establishment of a tolerable and pharmacologically active MTD/RP2D of BMS-986178 in the dose escalation and schedule and dose exploration sections, dose expansion in specific tumor cohorts will be initiated. Recent preclinical and clinical data will serve as the foundation for focusing on further optimizing the dose of BMS-986178 in combination with nivolumab.

Figure 3.1-1: Study Design Schematic (Parts 1 to 8)





Dose levels are specific for each part. Dose expansion will begin only after MTD/RP2D determination in the corresponding dose escalation phases of the study.

3.1.1 Study Outline (All Parts)

3.1.2 Dose Escalation (Parts 1A, 2A, and 3A)

The dose escalation part of the study will evaluate the safety and tolerability of BMS-986178 alone or in combination with nivolumab or ipilimumab in subjects with advanced solid tumors (listed in Section 3.3.1 [Inclusion criteria 2]).

The initial dose level of BMS-986178 planned for this study is 20 mg. Dose escalation decisions for subsequent doses will be based on DLTs using a BLRM (for BMS-986178 monotherapy) or a BLRM (-Copula) model (for BMS-986178 in combination with nivolumab or ipilimumab). The DLT period is 28 days for both monotherapy and combination therapy dose escalation parts. The DLT rate will be determined based on the incidence, severity, and duration of AEs that occur within the DLT period and for which no alternative cause can be identified. Dose selection for the next monotherapy cohort/dose level will take into account the BLRM (-Copula) recommendation (Section 3.1.2.4) in conjunction with clinical recommendation and all available PK, PD, immunogenicity, and clinical and laboratory safety data from all treated subjects. Starting dose selection of BMS-986178 for Part 2A will be determined using data available from Part 1A, including clinical and laboratory safety assessments, PK/PD data, immunogenicity, and modeling recommendation within Bayesian modeling framework by incorporating single-agent toxicity profiles of both BMS-986178 (Part 1A) and nivolumab (CA209003). Starting dose selection of BMS-986178 for Part 3A will be determined using data available from Parts 1A and 2A, including clinical and laboratory safety assessments, PK/PD data, and modeling recommendation within Bayesian modeling framework by incorporating single-agent toxicity profiles of both BMS-986178 (Part 1A) and ipilimumab (CA184022). The final dose escalation decision will be made after discussion and agreement between the investigators and the BMS Medical Monitor. Actual doses can be modified per the BLRM (-Copula) but will not exceed doubling of the previously tested dose. In Parts 2A and 3A, doses intermediate to previously tested doses or doses lower than the starting dose may be explored to further characterize the dose response for safety, PK, or PD as appropriate based on clinical data collected.

During dose escalation for all dose cohorts, the initial subject (sentinel subject) will be observed for 5 days before additional subjects in that cohort are treated with study drug.

All safety signals throughout the conduct of the study will be reviewed by the BMS-986178 Medical Surveillance Team (MST). If unexpected safety findings are identified between scheduled MST meetings, an ad hoc meeting will be convened, as appropriate.

Approximately 30 subjects will be enrolled in each dose escalation part. The number of subjects in each dose escalation cohort may vary depending on the BLRM (-Copula) recommendations. Initially, approximately 3 subjects will be treated at the starting dose levels of BMS-986178 or BMS-986178 in combination with nivolumab or ipilimumab. Additional cohorts of approximately 3 evaluable subjects will be treated at recommended dose levels per BLRM (-Copula) during the dose escalation phase. At least 6 DLT-evaluable subjects will be treated at the MTD.

3.1.2.1 Part 1A: Monotherapy Dose Escalation

Part 1A is BMS-986178 monotherapy dose escalation. The initial dose of BMS-986178 for Part 1A will be 20 mg with expected subsequent doses of 40, 80, 160, and 320 mg. Dosing of BMS-986178 will begin on Day 1 of each cycle and will be administered q2w for up to 12 cycles.

3.1.2.2 Part 2A: Combination with Nivolumab Dose Escalation

Part 2A is the combination arm of BMS-986178 with nivolumab that will be initiated only after at least 3 dose levels in the monotherapy dose escalation have been found to be tolerated or an MTD/RP2D has been determined in the monotherapy dose escalation (Part 1A). The starting dose of BMS-986178 in Part 2A will be at least 1 dose level below a dose that was demonstrated to be tolerated in Part 1A to ensure further safety of the combination. At no time will the dose for BMS-986178 in Part 2A exceed the highest tolerated dose in Part 1A. Nivolumab will be administered at a flat dose of 240 mg. Each treatment cycle will be 2 weeks in length and study drugs will be administered q2w starting on Day 1 of each cycle for up to 12 cycles.

3.1.2.3 Part 3A: Combination with Ipilimumab Dose Escalation

Part 3A is the combination arm of BMS-986178 with ipilimumab that will be initiated only after **at least** 3 dose levels in the monotherapy dose escalation have been found to be tolerated or an MTD/RP2D has been determined in the monotherapy dose escalation (Part 1A) **and** at least 1 dose cohort has been found to be tolerated in the BMS-986178 with nivolumab dose escalation part (Part 2A). The starting dose of BMS-986178 in Part 3A will be at least 1 dose level below a dose that was demonstrated to be tolerated in Part 1A. At no time will the dose for BMS-986178 in Part 3A exceed the highest tolerated dose in Part 1A to further ensure safety of the combination doses in treated subjects. Ipilimumab will be administered at a dose of 1 mg/kg. Each treatment cycle will be 3 weeks in length. BMS-986178 will be administered q3w starting on Cycle 1 Day 1, up to and including 8 cycles, and ipilimumab will be administered q3w starting on Day 1 for 4 cycles. Only BMS-986178 will be administered in the last 4 cycles.

3.1.2.4 BLRM Dose Escalation and Stopping Rules

In Parts 1A, 2A, and 3A, the BLRM and BLRM (-Copula) models (Section 1.1.13) will be utilized for dose escalation recommendations after DLT information becomes available for each cohort of subjects. BMS-986178 dose selection for the next cohort/dose level will take into account the BLRM (-Copula) recommendation in conjunction with clinical recommendation and all available PK, PD, and clinical and laboratory safety data from all treated subjects. The final dose escalation decision will be made after discussion and agreement between investigators and the BMS Medical Monitor.

BLRM Dose Escalation Rules (Parts 1A, 2A, and 3A)

Cohort tolerability assessment and subsequent dose recommendation will occur when 2 evaluable subjects within a dose cohort have completed the 28-day DLT period. If the potential DLT occurring in the third evaluable subject at a specific dose level does not influence the dose recommendation by BLRM (-Copula), the BLRM (-Copula)-recommended next dose level may proceed without waiting for the third subject to complete the corresponding DLT observation

period after discussion and agreement between the Sponsor and investigators. While waiting for the DLT information of those 2 or 3 subjects, if additional subjects are available, these subjects could be enrolled to the current dose level. Continuous re-assessment of dose recommendation by BLRM (-Copula) will be carried out at every dose level of each cohort of subjects, taking into consideration all available DLT information.

The BLRM (-Copula) model will first exclude doses that are intolerable (with overdosing probabilities > 25%). Among those qualified candidate doses that are considered "safe", the model will select the dose that maximizes the probability of being within the target toxicity range (DLT rate of 16% to up to 33%).

- Dose levels for the next cohort will be based on evaluating 4 potential recommendations: escalate, de-escalate, stay at same dose level, or stop and select a new dose other than pre-specified doses.
- Escalation by more than 1 dose level (dose skipping) is not permitted.
- Based on model suggestions and a review of the available safety, PK, and PD data in combination with clinical recommendation, lower doses of BMS-986178 may be tested if none of the planned doses are found to be tolerated as monotherapy or in combination with nivolumab or ipilimumab. Such decisions will be made after discussion and agreement between the investigators and the BMS Medical Monitor.
- No intra-subject dose escalation of BMS-986178 is allowed at any dose level.
- Dose de-escalation can be recommended by the model, and the final decision will be made based on clinical recommendation.

<u>BLRM Stopping Rules during Dose Escalation (Parts 1A, 2A, and 3A)</u>

- If all of the current pre-specified doses are considered intolerable according to the pre-specified cutoff, then the model will recommend stopping the current dose level and a new dose level lower than the current lowest dose level will need to be identified (EWOC stopping).
- The maximum number of subjects in a dose level will be 12. This limit is set to avoid instances in which the model could recommend adding subjects indefinitely to a specific dose level due to uncertainty in the tolerability profile.
- If, for a specific dose level, 6 subjects have been treated and the chance of determining that dose level to be the "target" dose is > 50%, then the model will suggest to stop the arm and declare the current dose level to be MTD.

Appendix 1 provides further detailed explanation along with an illustration of the BLRM dose escalation design.

3.1.2.5 Dose-Limiting Toxicity in Dose Escalation Parts

For the purpose of guiding dose escalation, DLTs will be defined based on the incidence, severity, and duration of AEs for which no clear alternative cause is identified. The DLT period will be 28 days after initial dosing in monotherapy and combination parts of dose escalation.

For the purpose of defining MTD/RP2D, the incidence of DLTs during the DLT period will be used. AEs occurring after the DLT period will be considered for the purposes of defining the RP2D

upon agreement between the Sponsor, Medical Monitor, and investigators, if they are determined to have no clear alternative cause and are not related to disease progression.

For the purpose of subject management, any AE that meets DLT criteria, regardless of the cycle in which it occurs, will lead to discontinuation of study drug. Subjects experiencing a DLT will not be retreated with study drug(s) and will enter the Safety Follow-up period of the study for up to 100 days from the last administration of the study drug(s). Subjects who withdraw from the study during the DLT evaluation interval for reasons other than a DLT may be replaced with a new subject at the same dose level.

Further details on DLTs are included in Section 4.5.1.

3.1.3 Schedule and Dose Exploration

3.1.3.1 Part 4: Combination with Nivolumab on a 4-week Schedule

Part 4 is the combination arm of BMS-986178 with nivolumab (480 mg) to be administered q4w. The dose of BMS-986178 will be a dose previously evaluated in Part 2A that has been found to have a manageable safety profile. If the starting dose of BMS-986178 is not tolerated or to further characterize the dose response for safety, PK, or PD as appropriate based on clinical data collected, a dose(s) lower or higher than the previously administered dose in this part may be explored. To further ensure safety of the combination, at no time will the dose for BMS-986178 in Part 4 exceed the highest tolerated dose in Part 2A, in which q2w dosing is explored. Approximately 6 to 12 subjects will be treated in this schedule and dose exploration cohort.

3.1.3.2 Part 5: Combination with Ipilimumab at 3 mg/kg

Part 5 is the combination arm of BMS-986178 with ipilimumab 3 mg/kg q3w for 4 doses, followed by monotherapy with BMS-986178 (maintenance therapy). The dose of BMS-986178 will be a dose previously evaluated in Part 3A that has been found to have a manageable safety profile. If the starting dose of BMS-986178 is not tolerated or to further characterize the dose response for safety, PK, or PD as appropriate based on clinical data collected, a dose(s) lower or higher than the previously administered dose in this part may be explored. To further ensure safety of the combination, at no time will the dose for BMS-986178 in Part 5 exceed the highest tolerated dose in Part 3A. Approximately 6 to 12 subjects will be treated in this schedule and dose exploration cohort.

3.1.3.3 Part 8: Dose Regimen Exploration of Combination with Nivolumab in Bladder Cancer

Part 8 is a dose regimen exploration of BMS-986178 in combination with nivolumab or nivolumab monotherapy. Nivolumab will be administered at a flat dose of 480 mg to be administered every 4 weeks.

Approximately 20 evaluable subjects per cohort will be treated in Part 8.

Part 8 Cohort 1-3: BMS-986178 will be administered as a flat dose of either 20 mg, 40 mg, or 80 mg q12w in combination with nivolumab flat dose (480 mg; q4w). Each treatment cycle will be 12 weeks in length starting on Day 1 of each cycle. There will be up to 9 cycles, to allow for

24 months of treatment. A tetanus vaccine (Tdap preferred, Td or equivalent after discussion with the medical monitor) will be administered first on Cycle 1 Day 1 prior to administration of nivolumab and BMS-986178.

Part 8 Cohort 4: Nivolumab monotherapy will be administered as a flat dose of 480 mg (q4w). Each treatment cycle will be 12 weeks in length and will be dosed for up to 9 cycles, 24 months of dosing. Treatment will be given on Day 1, Day 29 and 57 of each cycle. A tetanus vaccine (Tdap preferred, Td or equivalent after discussion with the medical monitor) will be administered first on Cycle 1 Day 1 prior to administration of nivolumab monotherapy.

3.1.4 Safety Cohorts

3.1.4.1 Part 6A: Combination with Nivolumab and Ipilimumab in RCC

Part 6A is the safety cohort for the combination of BMS-986178 with ipilimumab and nivolumab in subjects with RCC. BMS-986178 will be administered at a flat dose of 40 mg in combination with nivolumab (240 mg) and ipilimumab (1 mg/kg) q3w during Cycles 1 to 4, followed by maintenance therapy (Cycle 5 and beyond) in which BMS-986178 (40 mg) and nivolumab (480 mg) will be administered q4w. Study drugs will be administered accordingly starting on Day 1 of each cycle. If the starting dose of BMS-986178 is not tolerated or to further characterize the dose response for safety, PK, or PD as appropriate based on clinical data collected, a dose(s) lower than the previously administered dose in this part may be explored. Approximately 6 to 12 subjects will be treated in this safety cohort.

3.1.4.2 Part 7A: Combination with Nivolumab and Ipilimumab in NSCLC

Part 7A is the safety cohort for the combination of BMS-986178 with ipilimumab and nivolumab in subjects with NSCLC. BMS-986178 will be administered at a flat dose of 40 mg (q2w) in combination with nivolumab (240 mg; q2w) and ipilimumab (1 mg/kg; q6w) for four 6-week cycles. Study drugs will be administered accordingly starting on Day 1 of each cycle. If the starting dose of BMS-986178 is not tolerated or to further characterize the dose response for safety, PK, or PD as appropriate based on clinical data collected, a dose(s) lower than the previously administered dose in this part may be explored. If subjects continue for additional cycles, past cycle 4, all study drugs (BMS-986178/nivolumab/ipilimumab) will continue for all cycles. Approximately 6 to 12 subjects will be treated in this safety cohort.

3.1.5 Dose Expansion Parts (Parts 2B, 2C, 2D, 2E, 3B, 3C, 6B, and 7B)

Treatment in the dose expansion cohorts will be initiated when the MTD/RP2D(s) has been determined based on the evaluation of totality of available clinical safety (DLTs, AEs occurring after the DLT period), PK, PD, immunogenicity, and modeling data from the dose escalation parts (1A, 2A, and 3A) or schedule and dose exploration parts (4 and 5). Mandatory pre- and on-treatment biopsies of tumor will be obtained for all study subjects.

3.1.5.1 Part 2B: Combination with Nivolumab Dose Expansion in Colorectal Cancer

Part 2B is the combination therapy (BMS-986178 with nivolumab) dose expansion part in subjects with CRC at the MTD/RP2D(s) determined in Parts 2A or 4. Nivolumab will be administered at a

flat dose of 240 or 480 mg. Each treatment cycle will be either 2 (240 mg) or 4 (480 mg) weeks in length and study drugs will be administered every 2 or 4 weeks starting on Day 1 of each cycle for up to 12 or 6 cycles, respectively. Approximately 35 subjects will be treated in this expansion cohort.

3.1.5.2 Part 2C: Combination with Nivolumab Dose Expansion in Bladder Cancer

Part 2C is the combination therapy (BMS-986178 with nivolumab) dose expansion part in subjects with BC at the MTD/RP2D(s) determined in Parts 2A or 4. Nivolumab will be administered at a flat dose of 240 or 480 mg. Each treatment cycle will be either 2 (240 mg) or 4 (480 mg) weeks in length and study drugs will be administered every 2 or 4 weeks starting on Day 1 of each cycle for up to 12 or 6 cycles, respectively. Approximately 27 subjects will be treated in this expansion cohort.

3.1.5.3 Part 2D: Combination with Nivolumab Dose Expansion in Cancer of the Cervix

Part 2D is the combination therapy (BMS-986178 with nivolumab) dose expansion part in subjects with cervical cancer at the MTD/RP2D(s) determined in Part 2A or 4. Nivolumab will be administered at a flat dose of 240 or 480 mg. Each treatment cycle will be either 2 (240 mg) or 4 (480 mg) weeks in length and study drugs will be administered every 2 or 4 weeks starting on Day 1 of each cycle for up to 12 or 6 cycles, respectively. Approximately 37 subjects will be treated in this expansion cohort.

3.1.5.4 Part 2E: Combination with Nivolumab Dose Expansion in Other Tumors for Signal Finding

Part 2E is the combination therapy (BMS-986178 with nivolumab) dose expansion part at the MTD/RP2D(s) determined in Part 2A or 4. Nivolumab will be administered at a flat dose of 240 or 480 mg. Each treatment cycle will be either 2 (240 mg) or 4 (480 mg) weeks in length and study drugs will be administered every 2 or 4 weeks starting on Day 1 of each cycle for up to 12 or 6 cycles, respectively. Approximately 40 subjects will be treated in this expansion cohort.

Tumor types for this cohort will be selected by Sponsor from those permitted in dose escalation which do not have a dedicated expansion cohort or plans for evaluation in other studies and those tumors selected will be communicated to the investigators. This cohort will allow for further exploration of early signs of clinical activity observed in tumors during the dose escalation phase of the trial as well as potential signals arising from ongoing trials of other anti OX40 agonists in combination with anti-PD(L)-1. Subjects enrolled in this cohort must be refractory to or intolerant of established therapy known to provide clinical benefit for their condition, i.e., subjects must not be candidates for regimens known to provide clinical benefit.

3.1.5.5 Part 3B: Combination with Ipilimumab Dose Expansion in Ovarian Cancer

Part 3B is the combination therapy (BMS-986178 with ipilimumab) dose expansion part in subjects with OC at the MTD/RP2D(s) determined in Part 3A or 5. Each treatment cycle will be

3 weeks in length. Ipilimumab will be administered in the initial 4 cycles in combination with BMS-986178. Then the subject will continue on BMS-986178 monotherapy for up to an additional 4 cycles for a total of up to 24 weeks (8 cycles) of treatment. Approximately 35 subjects with OC will be treated in this expansion cohort.

3.1.5.6 Part 3C: Combination with Ipilimumab Dose Expansion in Other Tumors for Signal Finding

Part 3C is the combination therapy (BMS-986178 with ipilimumab) dose expansion part in subjects with other tumors from dose escalation for signal finding at the MTD/RP2D(s) determined in Part 3A or 5. Each treatment cycle will be 3 weeks in length. Ipilimumab will be administered in the initial 4 cycles in combination with BMS-986178. Then the subject will continue on BMS-986178 monotherapy for up to an additional 4 cycles for a total of up to 24 weeks (8 cycles) of treatment. Approximately 40 subjects will be treated in this expansion cohort.

Tumor types for this cohort will be selected by Sponsor from those permitted in dose escalation which do not have a dedicated expansion cohort or plans for evaluation in other studies and those selected tumors will be communicated to the investigators. This cohort will allow for further exploration of early signs of clinical activity observed in tumors during the dose escalation phase of the trial as well as potential signals arising from ongoing trials of other anti OX40 agonists in combination with anti-CTLA-4. Subjects enrolled in this cohort must be refractory to or intolerant of established therapy known to provide clinical benefit for their condition, i.e., subjects must not be candidates for regimens known to provide clinical benefit.

3.1.5.7 Part 6B: Combination with Nivolumab and Ipilimumab in Renal Cell Carcinoma

Part 6B is the combination therapy (BMS-986178, nivolumab, and ipilimumab) dose expansion part in subjects with RCC at a dose determined to be tolerated in Part 6A. BMS-986178 will be administered at the RP2D(s) in combination with nivolumab (240 mg) and ipilimumab (1 mg/kg) q3w during Cycles 1 to 4 followed by maintenance therapy (Cycle 5 and beyond) in which BMS-986178 and nivolumab (480 mg) will be administered q4w. Study drugs will be administered accordingly starting on Day 1 of each cycle. Approximately 40 subjects will be treated in this expansion cohort.

3.1.5.8 Part 7B: Combination with Nivolumab and Ipilimumab in Non-small Cell Lung Cancer

Part 7B is the combination therapy (BMS-986178, nivolumab, and ipilimumab) dose expansion part in subjects with NSCLC at a dose determined to be tolerated in Part 7A. BMS-986178 will be administered at the RP2D(s) (q2w) in combination with nivolumab (240 mg; q2w) and ipilimumab (1 mg/kg; q6w) for four, 6-week cycles. Study drugs will be administered accordingly starting on Day 1 of each cycle. If subjects continue for additional cycles, past Cycle 4, all study drugs (BMS-986178/nivolumab/ipilimumab) will continue for all cycles. Approximately 40 subjects will be treated in this expansion cohort.

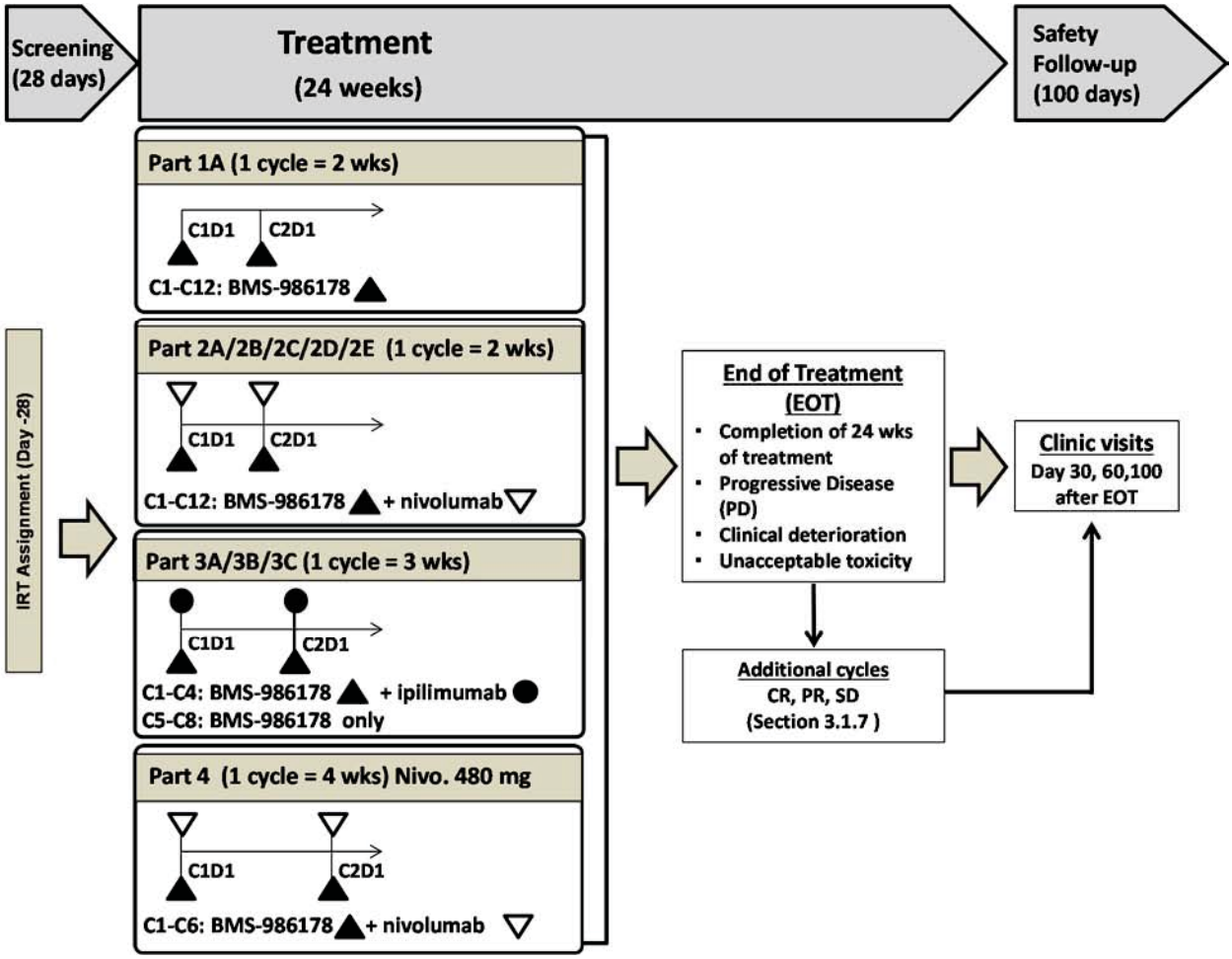
3.1.5.9 Stopping Rules during Dose Expansion

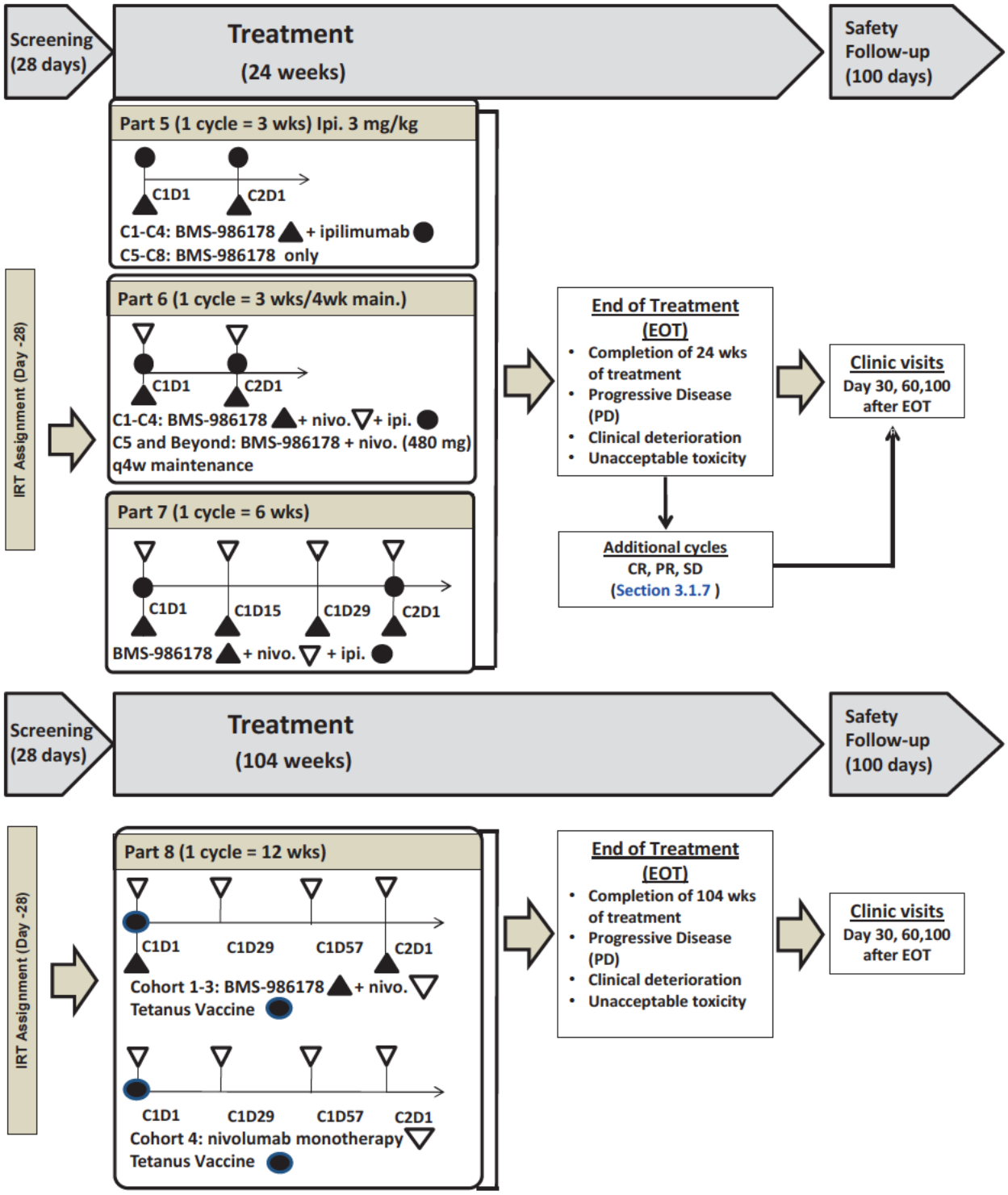
- Evaluation of toxicity will be performed throughout enrollment in the dose expansion cohorts.
- If the rate of DLTs exceeds 33% in any cohort, the findings will be discussed between the investigators and Sponsor, and further enrollment may be interrupted in that expansion cohort.
- If an expansion cohort is discontinued due to toxicity, a new cohort at a previously tested lower dose level may be considered based on the aggregate safety experience and in consultation and agreement between the investigators and Sponsor.
- During dose expansion, a specific cohort may be stopped due to lack of efficacy per Simon 2-stage design recommendation.[154,155] Due to the heterogeneous nature of tumor responses seen with immunotherapy (eg, late responses), such a decision would not be strictly based on the number of responses but would include all available efficacy data.
- The non-binding nature of stopping boundaries allows for flexibility of examination on the totality of data to determine the risk/benefit ratio.

3.1.6 Study Schedule

In all cohorts, subjects will complete: Screening (up to 28 days), Treatment (up to 24 weeks [Part 1-7], until meeting protocol-specified discontinuation criteria), and Safety Follow-up (approximately 100 days), as described below. Screening and the Treatmentperiod are calculated relative to the first dose of study drug, while Safety Follow-up periods are calculated relative to the last dose. The study visit schematic is presented in Figure 3.1.6-1. The study will end when the last subject completes their last study visit, which is planned to be about 4 years after the start of the study. Part 8 subjects will receive treatment up to 24 months. Safety Follow-up period will be approximately 100 days from the end of treatment.

Figure 3.1.6-1: Study Visit Schematic





Abbreviations: CR = complete response; EOT = end of treatment; Ipi = ipilimumab; IRT = Interactive Response Technology; Nivo = nivolumab; PD = progressive disease; PR = partial response; SD = stable disease; wks = weeks.

3.1.6.1 Screening Period

The screening period will last for up to 28 days. The screening period begins by establishing the subject's initial eligibility and signing of the ICF. Subjects will be enrolled using an Interactive Response Technology (IRT).

If a subject surpasses the 28-day window during the screening period due to a study-related procedure (eg, scheduling of a tumor biopsy or waiting time for a study-related laboratory value), the subject must be re-consented, but does not need to be assigned a new subject identification number. In this situation, the fewest number of procedures from the initial screening should be repeated to qualify the subject, while maintaining safety and eligibility under the discretion of the BMS Medical Monitor and investigator, to reduce any undue burden of procedures in this subject population.

3.1.6.2 Treatment Period

Eligible subjects will be assigned to the open parts/cohorts by IRT (see Section 4.4).

The treatment period consists of up to 24 weeks of dosing for Part 1-7. Part 8 will have a treatment period up to 24 months of dosing.

Following each treatment cycle, the decision to treat a subject with the next cycle of study therapy, up to 24 weeks of treatment or Part 8 up to 24 months, will be based on risk/benefit and tumor assessments. Tumor assessments will be performed every 8 weeks for Part 1-7 or every 12 weeks for Part 8 (± 1 week). Assessments of partial response (PR) and complete response (CR) must be confirmed at least 4 weeks following initial assessment. Tumor progression or response endpoints will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 3).

Subjects with a response of SD, PR, or CR at the end of a given cycle will continue to the next treatment cycle. Subjects will generally be allowed to continue study therapy until the first occurrence of one of the following: 1) completion of the maximum number of cycles; 2) PD; 3) clinical deterioration suggesting that no further benefit from treatment is likely; 4) intolerability to therapy; or 5) the subject meets criteria for discontinuation of study therapy as outlined in Section 4.5.6. Individual subjects with confirmed CR will be given the option to discontinue study therapy on a case-by-case basis after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where risk/benefit justify discontinuation of study therapy.

Approximately 604 subjects will be enrolled, and approximately 515 subjects will be treated in the study.

3.1.6.3 Safety Follow-up

Upon completion of study therapy, subjects will enter the Safety Follow-up period.

After the end of treatment (EOT) visit, subjects will be evaluated for any new AEs for at least 100 days after the last dose of therapy. Follow-up visits should occur at Days 30, 60, and 100 after the last dose or the date of discontinuation. Subjects (except those who withdraw consent for study

participation) are expected to complete the 3 clinical Safety Follow-up visits regardless of whether they start new anti-cancer therapy.

For subjects who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit, and the start of Week 1 Safety Follow-up visit. For subjects who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data); the visit does not need to be repeated and will be considered the start of the Safety Follow-up period.

3.1.7 Treatment with Additional Cycles

Part 1-7 subjects will be treated for 24 weeks unless criteria for study drug discontinuation are met earlier (Section 4.5.6). Subjects in Parts 2, 4, 6, and 7 completing approximately 24 weeks of treatment with ongoing disease control (CR, PR, or SD) may be eligible for an additional 18 months of study therapy beyond the initial 24 weeks, on a case-by-case basis, after discussion and agreement with the BMS Medical Monitor that the risk/benefit assessment favors continued administration of study therapy. Upon completion of the additional 18 months of study therapy, subjects will enter Safety Follow-up period. Part 8 subjects will not be eligible for treatment with additional cycles. The maximum treatment allowed for any subject is 2 years from the first dose of study treatment regardless of dose delays.

Parts 3 and 5 subjects completing approximately 24 weeks of treatment with ongoing disease control (CR, PR, or SD) may be eligible for an additional 24 weeks of study therapy beyond the initial 24 weeks, on a case-by-case basis, after discussion and agreement with the BMS Medical Monitor that the risk/benefit assessment favors continued administration of study therapy. Upon completion of the additional 24 weeks of study therapy, subjects will enter Safety Follow-up period.

3.1.8 Treatment Beyond Progression

Treatment beyond progression may be allowed in select subjects with initial RECIST v1.1-defined progressive disease after discussion and agreement with the BMS Medical Monitor that the benefit/risk assessment favors continued administration of study therapy (eg, subjects are continuing to experience clinical benefit as assessed by the investigator, tolerating treatment, and meeting other criteria specified in (Section 3.5.1).

Subjects must be re-consented with an Informed Consent Form addendum to continue treatment beyond progression.

3.2 Post-study Access to Therapy

At the end of the study, BMS will not continue to provide BMS-supplied study drug to subjects and investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate SOC to treat the condition under study.

3.3 Study Population

For entry into the study, the following criteria MUST be met prior to dosing on Day 1. No exceptions will be granted.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent
   a) The subject must sign the ICF prior to the performance of any study-related procedures that are not considered part of SOC.
   b) Consent for tumor biopsy samples (mandatory pre- and on-treatment biopsies) are required for all subjects enrolled.
2) Target Population

   Subjects must be at least 18 years old and have histologic or cytologic confirmation of a malignancy that is advanced (metastatic, recurrent, refractory, and/or unresectable) with measurable disease per RECIST v1.1 (see Appendix 3).

   1) **Dose Escalation/Schedule and Dose Exploration/Safety Cohorts/Dose Expansion (Part 2E/3C)** Subjects must be refractory to or intolerant of established therapy known to provide clinical benefit for their condition, i.e., subjects must not be candidates for regimens known to provide clinical benefit.

      The following tumor histologies will be permitted except for subjects with primary central nervous system (CNS) tumors, or with CNS metastases as the only site of active disease.

      Parts 1A, 2A, 2E, 3A, 3C, 4, and 5

      (i) Melanoma: BRAF mutation status must be documented if known

      (ii) NSCLC: EGFR, anaplastic lymphoma kinase (ALK), KRAS, and ROS1 mutational status must be documented if known

      (iii) Head and neck cancer restricted to squamous cell carcinoma: HPV status must be documented if known

      (iv) Transitional cell carcinoma of the genitourinary tract

      (v) Renal cell carcinoma

      (vi) Pancreatic adenocarcinoma

      (vii) CRC: MSI, KRAS, and BRAF status must be documented if known

      (viii) Cervical cancer: HPV status must be documented if known

      (ix) Triple negative breast cancer HER2, ER, and PR status must be documented

      (x) Adenocarcinoma of the endometrium

      (xi) Ovarian cancer

      (xii) Prostate adenocarcinoma

      (xiii) Hepatocellular cancer-Child Pugh A only

      (xiv) Small cell lung cancer

(xv) Gastric and gastric esophageal junction cancer: HER2 status must be documented if known

(xvi) Thyroid cancer

Part 6A (RCC)

(xvii) Subjects with histological confirmation of RCC with a clear-cell component

(xviii) Subjects must have received at least 1, but no more than 2, prior systemic therapies in the advanced/metastatic setting.

Part 7A (NSCLC)

Subjects must have histologic or cytologic confirmation of NSCLC (per the seventh International Association for the Study of Lung Cancer [IASLC][156]) with squamous or nonsquamous histology that is advanced (metastatic and/or unresectable).

(xix) Subjects must have had at least 1, but no more than 2, prior systemic therapies for NSCLC. Maintenance, adjuvant, or neoadjuvant (chemotherapy or chemoradiation) therapy does not count as an additional line of treatment.

(xx) Subjects should have been offered a platinum-based chemotherapy for NSCLC. The platinum-based chemotherapy may have been in the adjuvant, neoadjuvant, or recurrent setting. Prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least 4 weeks prior to enrollment.

(xxi) Prior definitive chemoradiation for locally advanced disease is also permitted as long as the last administration of chemotherapy or radiotherapy (whichever was given last) occurred at least 4 weeks prior to enrollment.

(xxii) Subjects with known EGFR mutations or ALK rearrangements must have received EGFR or ALK inhibitors, respectively.

(xxiii) EGFR, ALK, KRAS, ROS1 mutational status must be documented if known.

2) **Dose Expansion: Parts 2B, 2C, 2D, 3B, 6B, and 7B**

The following tumor types will be permitted:

(a) **Cervical Cancer - Part 2D**

(i) Histologically confirmed cervical cancer that is unresectable, metastatic, or recurrent with documented disease progression

(ii) Document tumor HPV status if known. If tumor HPV status is unknown, subjects must consent to allow their submitted archived tumor tissue sample (block or unstained slides) to be tested.

(iii) Prior therapy requirement:

- Subjects must have been offered and/or have received or refused at least 1 prior platinum-based therapy for metastatic and/or unresectable disease. Subjects must have not received more than 2 prior systemic therapies. Reason(s) for refusal should be documented. Concurrent chemotherapy administered with primary radiation and adjuvant chemotherapy given following completion of radiation therapy do not count as systemic therapies, though patients who progressed less than 6 months from primary platinum-based therapy are eligible.

(b) Colorectal Cancer - Part 2B

(i) Histologically confirmed CRC that is metastatic or recurrent with documented disease progression

(ii) Document MSI, MMR, KRAS, and BRAF status if known. If unknown, subjects must consent to allow their submitted archived tumor tissue sample (block or unstained slides) to be tested.

(iii) Prior therapy requirement:

Subjects must have received at least 1, but no more than 3, prior systemic therapies for metastatic and/or unresectable disease (or have progressed within 6 months of adjuvant therapy).

(c) Bladder Cancer - Part 2C

(i) Histologically or cytologically confirmed urothelial carcinoma (including mixed histologies of urothelial carcinoma with elements of other subtypes) of the renal pelvis, ureter, bladder, or urethra with progression or refractory disease

(ii) Prior therapy requirement:

Subjects must have been offered and/or have received or refused 1 prior platinum-based therapy for the treatment of metastatic or locally advanced unresectable disease. Subjects must have not received more than 2 prior systemic therapies. Reason(s) for refusal should be documented.

(d) Ovarian - Part 3B

(i) Histologically or cytologically confirmed ovarian carcinoma (including epithelial OC, primary peritoneal, or fallopian tube carcinoma) with documented disease progression

(ii) Documented germline BRCA mutation status, if known. If unknown, subjects must consent to allow their submitted archived tumor tissue sample (block or unstained slides) to be tested.

(iii) Prior therapy requirement:

Subjects must have received no more than 3 prior systemic therapies. One regimen must have been a prior platinum-based chemotherapy regimen for primary disease, possibly including intra-peritoneal therapy consolidation, biologic/targeted (non-cytotoxic) agents, or extended therapy (maintenance/consolidation) administered after surgical or non-surgical assessment. Patients must have progressed less than 12 months after completion of their last platinum-based chemotherapy. The number of months (platinum-free interval) should be calculated from the date of the last administered dose of platinum therapy to the date of the documentation of progression.

(e) RCC (Part 6B)

(i) Subjects with histologically confirmed RCC with a clear-cell component

(ii) Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC

(iii) No prior systemic therapy for RCC with the following exception:

One prior adjuvant or neoadjuvant therapy for completely resectable RCC if such therapy did not include an agent that targets VEGF or VEGF receptors and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy.

(iv) Subjects with favorable-, intermediate-, and poor-risk categories will be eligible for the study. Subjects must be categorized according to favorable- versus intermediate-/poor-risk status at registration according to the International Metastatic RCC Database Consortium (IMDC) criteria (Appendix 5).

(f) NSCLC (Part 7B)

(i) Subjects with histologically confirmed Stage IV or recurrent NSCLC (per the 7th IASLC) squamous or nonsquamous histology, with no prior systemic anticancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease.

(ii) Prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least 6 months prior to enrollment.

(iii) Prior definitive chemoradiation for locally advanced disease is also permitted as long as the last administration of chemotherapy or

radiotherapy (which ever was given last) occurred at least 6 months prior to enrollment.

(g) Bladder (Part 8)

(i) Histologically or cytologically confirmed urothelial carcinoma (including mixed histologies of urothelial carcinoma with elements of other subtypes) of the renal pelvis, ureter, bladder, or urethra with progression or refractory disease.

(ii) Subjects will need to have a pre-treatment and 2 on-treatment biopsies.

(iii) Prior therapy requirement:

Subjects must have been offered and/or have received or refused 1 prior platinum-based therapy for the treatment of metastatic or locally advanced unresectable disease. Subjects must have not received more than 1 prior systemic therapy. Reason(s) for refusal should be documented.

Subjects must be immunotherapy treatment naïve (eg, no prior therapy with experimental anti-tumor vaccines; any T-cell co-stimulation or checkpoint pathways, such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, including ipilimumab; or other medicines specifically targeting T-cells).

(iv) Within 12 months of peri-operative (neo-adjuvant or adjuvant) treatment with a platinum agent in the setting of cystectomy for localized muscle-invasive urothelial cancer.

(v) Sequential chemotherapy given as a planned sequence to optimize response will count as 1 regimen.

(vi) Vaccines for infectious disease (e.g., influenza) allowed, provided they are administered ≥ 2 weeks prior to or ≥ 2 weeks after study treatment/vaccine.

3) Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1
4) Presence of at least 1 lesion with measurable disease as defined by RECIST v1.1 for response assessment. Subjects with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided the lesion(s) have demonstrated clear progression and can be measured accurately.
5) All subjects require a fresh tumor biopsy, these subjects must have at least one lesion accessible for pre- and on-treatment biopsy, in addition to the minimum one RECIST v1.1 measureable lesion required for response assessment. This lesion needs to be distinct from index lesion(s) being evaluated for radiological response.
6) Parts 1-7 subjects with prior exposure to therapy with any agent specifically targeting checkpoint pathway inhibition (such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-LAG-3, and

anti-CTLA-4 antibody) are permitted after a washout period of any time greater than 4 weeks from the last treatment.

Note: *(i) Subjects who experienced prior Grade 1 to 2 checkpoint therapy-related immune-mediated AEs must have confirmed recovery from these events at the time of study entry,* ***other than endocrinopathies treated with supplementation****, as documented by resolution of all related clinical symptoms, abnormal findings on physical examination, and/or associated laboratory abnormalities. Where applicable, these subjects must also have completed steroid tapers for treatment of these AEs by a minimum of 14 days prior to commencing treatment with study therapy.*

(ii) Eligibility of subjects with prior ≥ Grade 3 checkpoint therapy-related immune AEs, will be considered on a case-by-case basis after discussion and agreement between the investigators and the medical monitor (eg, asymptomatic isolated Grade 3 lipase elevations without clinical or radiological features of pancreatitis will be permitted to enroll).

7) Prior palliative radiotherapy must have been completed at least 2 weeks prior to first dose of study drug. Subjects with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of first dose of study drug are strongly encouraged to receive palliative radiotherapy prior to enrollment.
8) **All Subjects** must consent to the acquisition of fresh pre- and on-treatment tumor biopsies for performance of correlative biomarker studies. Archival specimens may not be substituted for fresh baseline specimens but can be submitted to help understand the evolution of the tumor (ie, PD-L1 expression changes over time) for performance of correlative studies. Subjects who either do not consent to a pre-treatment tumor biopsy or do not have accessible lesions are not eligible. (However, subjects whose pre-treatment biopsy yields inadequate tissue quantity or quality will not be ineligible on this basis alone).
9) **All Subjects enrolled** will be required to undergo mandatory pre- and on-treatment biopsies at acceptable clinical risk as judged by the investigator.
    (a) The solid tumor tissue specimen must be a core needle, excisional, or incisional biopsy. Fine needle biopsies, drainage of pleural effusions with cytospins, or punch biopsies are not considered adequate for biomarker review. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable.
    (b) Biopsied lesions should be distinct from index lesion(s) being evaluated for radiological response
10) Adequate organ function for subjects as defined by the following:
    (a) Neutrophils ≥ 1500/μL
    (b) Platelets ≥ 80×10^3/μL (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)
    (c) Hemoglobin ≥ 8 g/dL (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)
    (d) ALT and AST ≤ 3× upper limit of normal (ULN)

(e) Total bilirubin ≤ 1.5 × ULN (except subjects with Gilbert's Syndrome who must have normal direct bilirubin)

(f) Normal thyroid function or stable on hormone supplementation, per investigator assessment

(g) Albumin ≥ 2 g/dL

(h) Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CrCl) ≥ 40 mL/min (measured using the Cockcroft-Gault formula below):

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

11) Ability to comply with treatment, PK, and PD sample collection and required study follow-up

Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (eg, subject has not been treated). If re-enrolled, the subject must be re-consented.

3) Age and Reproductive Status

a) Men and women, ages ≥ 18 years at the time of informed consent

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotrophin [hCG]) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug BMS-986178 plus 5 half-lives of study drug plus 30 days. This duration should be 12 weeks for Parts 1 and 3 subjects (50 days plus 30 days) or 5 months for Part 2 subjects (130 days plus 30 days [duration of ovulatory cycle]), for a total of up to 160 days post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug BMS-986178 plus 5 half-lives of the study drug plus 90 days. The duration should be 20 weeks for Parts 1 and 3 subjects (50 days plus 90 days) or 7 months for Part 2 subjects (130 days plus 90 days [duration of sperm turnover]), for a total of up to 220 days post-treatment completion. In addition, male subjects must be willing to refrain from sperm donation during this time.

f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, but must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception, which have a failure rate of < 1% when used consistently and correctly.

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects who are WOCBP are expected to use one of the highly effective methods of contraception (listed below). Local laws and regulations may require use of alternative and/or additional contraception methods. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Male subjects are expected to use a condom, in addition to a highly effective method as noted in the list below:

1. Progestogen only hormonal contraception associated with inhibition of ovulation
2. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen and progesterone, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena®
3. Nonhormonal IUDs, such as ParaGard®
4. Bilateral tubal occlusion
5. Vasectomized partner with documented azoospermia 90 days after procedure
    - Vasectomy is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
6. Intrauterine hormone-releasing system
7. Complete abstinence
    - Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms)
    - Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the study drug(s) plus 30 days).
    - It is not necessary to use any other method of contraception when complete abstinence is elected.
    - Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 5.1.
    - Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
    - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
8. Use a condom in male subjects with female partners.

UNACCEPTABLE METHODS OF CONTRACEPTION

1) Periodic abstinence (calendar, symptothermal, and/or post-ovulation methods)
2) Withdrawal (coitus interruptus)
3) Spermicide only
4) Lactation amenorrhea method
5) Diaphragm with spermicide
6) Cervical cap with spermicide
7) Vaginal sponge with spermicide
8) Male or female condom with or without spermicide*
9) Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.

* A male and a female condom must not be used together.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Subjects with known or suspected CNS metastases or untreated CNS metastases, or with the CNS as the only site of disease, are excluded. However, subjects with controlled brain metastases will be allowed to enroll. Controlled brain metastases are defined as no radiographic progression for at least 4 weeks following radiation and/or surgical treatment (or 4 weeks of observation if no intervention is clinically indicated), and off of steroids for at least 2 weeks, and no new or progressive neurological signs and symptoms.

b) Subjects with carcinomatous meningitis

c) For ovarian cancer (Part 3B):

i) Ovarian cancer subjects with history of bowel obstruction in the prior 6 months or with intraperitoneal catheter (eg.Tenckhoff) will be excluded.

ii) Not applicable

d) For NSCLC (Part 7B)

i) Subjects with known EGFR mutations, which are sensitive to available targeted inhibitor therapy (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution mutations), are excluded. All subjects with non-squamous histology must have been tested for EGFR mutation status; use of an FDA-approved test is strongly encouraged. Subjects with non-squamous histology and unknown or indeterminate EGFR status are excluded.

ii) Subjects with known ALK translocations, which are sensitive to available targeted inhibitor therapy, are excluded. If tested, the use of an FDA-approved test is strongly encouraged. Subjects with unknown or indeterminate ALK status may be enrolled.

e) For Bladder Cancer (Part 8)

i) Prior therapy with experimental anti-tumor vaccines, any T-cell co-stimulation or checkpoint pathways, such as anti-PD1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, including ipilimumab, or other medicines specifically targeting T-cells is also prohibited in this part of the study.

ii) No prior adverse reaction to tetanus toxoid-containing vaccines.

iii) Subjects with known allergies to egg products, neomycin, or tetanus toxoid are also considered ineligible.

2) Medical History and Concurrent Diseases

a) Subjects with a prior malignancy, different from the one used for enrollment in this study, diagnosed within less than 2 years prior to study entry are excluded (except non-melanoma skin cancers and in situ cancers such as bladder, colon, cervical/dysplasia, melanoma, or breast). In addition, subjects with other second malignancies diagnosed more than 2 years ago who have received therapy with curative intent with no evidence of disease during the interval who are considered by the investigator to present a low risk for recurrence will be eligible.

b) Subjects with other active malignancy requiring concurrent intervention are excluded.

c) Prior organ allograft

d) Previous treatment:

i) Prior anti-cancer treatments are permitted (ie, chemotherapy, radiotherapy, hormonal, or immunotherapy) except in Parts 6B (Inclusion criteria 1.a)(1)2)(e)) and 7B (Inclusion criteria 1.a)(1)2)(f)).

ii) Toxicity (except for alopecia) related to prior anti-cancer therapy and/or surgery must either have resolved, returned to baseline or Grade 1, or have been deemed irreversible.

iii) For cytotoxic agents, at least 4 weeks must have elapsed between the last dose of prior anti-cancer therapy and initiation of study therapy.

iv) For non-cytotoxic agents, at least 4 weeks or 5 half-lives (whichever is shorter) must have elapsed from last dose of prior anti-cancer therapy and the initiation of study therapy. If 5 half-lives is shorter than 4 weeks, agreement with Sponsor/medical monitor is mandatory.

e) Subjects with prior therapy with any agent specifically targeting T-cell co-stimulation pathways such as anti-OX40 antibody, anti-CD137, anti-GITR antibody, and anti-CD27 are excluded.

f) Subjects with active, known, or suspected autoimmune disease are excluded. Subjects with vitiligo, type 1 diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, euthyroid subjects with a history of Grave's disease (subjects with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin prior to first dose of study drug), psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. Subjects with well controlled asthma and/or mild allergic rhinitis (seasonal allergies) are eligible.

g) Subjects with history of life-threatening toxicity related to prior immune therapy (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after adrenal crisis)

h) Subjects with interstitial lung disease that is symptomatic or that may interfere with the detection or management of suspected drug-related pulmonary toxicity

i) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration except for adrenal replacement steroid doses > 10 mg daily prednisone equivalent in the absence of active autoimmune disease. **Note**: Treatment with a short course of steroids (< 5 days) up to 7 days prior to initiating study drug is permitted.

j) Uncontrolled or significant cardiovascular disease, including but not limited to any of the following:

   i) Myocardial infarction or stroke/transient ischemic attack within the past 6 months

   ii) Uncontrolled angina within the past 3 months

   iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)

   iv) History of other clinically significant heart disease (eg, cardiomyopathy, myocarditis, congestive heart failure with New York Heart Association functional classification III-IV, pericarditis, significant pericardial effusion)

   v) Cardiovascular disease-related requirement for daily supplemental oxygen therapy

   vi) QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation > 480 msec

k) History of any chronic hepatitis as evidenced by the following:

   i) Positive test for hepatitis B surface antigen

   ii) Positive test for qualitative hepatitis C viral load (by polymerase chain reaction [PCR])

   Note: Subjects with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible. History of resolved hepatitis A virus infection is not an exclusion criterion.

   Additional testing or substitute testing per institutional guidelines to rule out infection is permitted.

l) Evidence of active infection that requires systemic antibacterial, antiviral, or antifungal therapy ≤ 7 days prior to initiation of study drug therapy (does not apply to viral infections that are presumed to be associated with the underlying tumor type required for study entry)

m) Known history of testing positive for HIV or known acquired immunodeficiency syndrome. **Note:** Testing for HIV must be performed at sites where mandated by local requirements.

n) Any major surgery within 4 weeks of study drug administration. Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study drug.

o) Use of non-oncology vaccines containing live virus for prevention of infectious diseases within 4 weeks prior to study drug. The use of inactivated seasonal influenza vaccines, eg, Fluzone®, will be permitted on study without restriction.

p) Use of packed red blood cell or platelet transfusion within 2 weeks prior to the first dose of study drug

q) A known or underlying medical or psychiatric condition and/or social reason that, in the opinion of the investigator or Sponsor, could make the administration of study drug hazardous to the subject or could adversely affect the ability of the subject to comply with or tolerate the study.

3) Allergies and Adverse Drug Reaction

a) History of allergy to nivolumab or ipilimumab (Parts 2 and 4 or 3 and 5, respectively) or history of allergy to the combination of nivolumab and ipilimumab (Parts 6 and 7)

b) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity) to prior anti-cancer immune modulating therapies (eg, checkpoint inhibitors, T-cell co-stimulatory antibodies)

4) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances, a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply, and BMS approval is required.)

b) Subjects who are compulsorily detained for the treatment of either psychiatric or physical (eg, infectious disease) illness

c) Inability to comply with restrictions and prohibited activities/treatments as listed in Section 3.4

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a documented serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

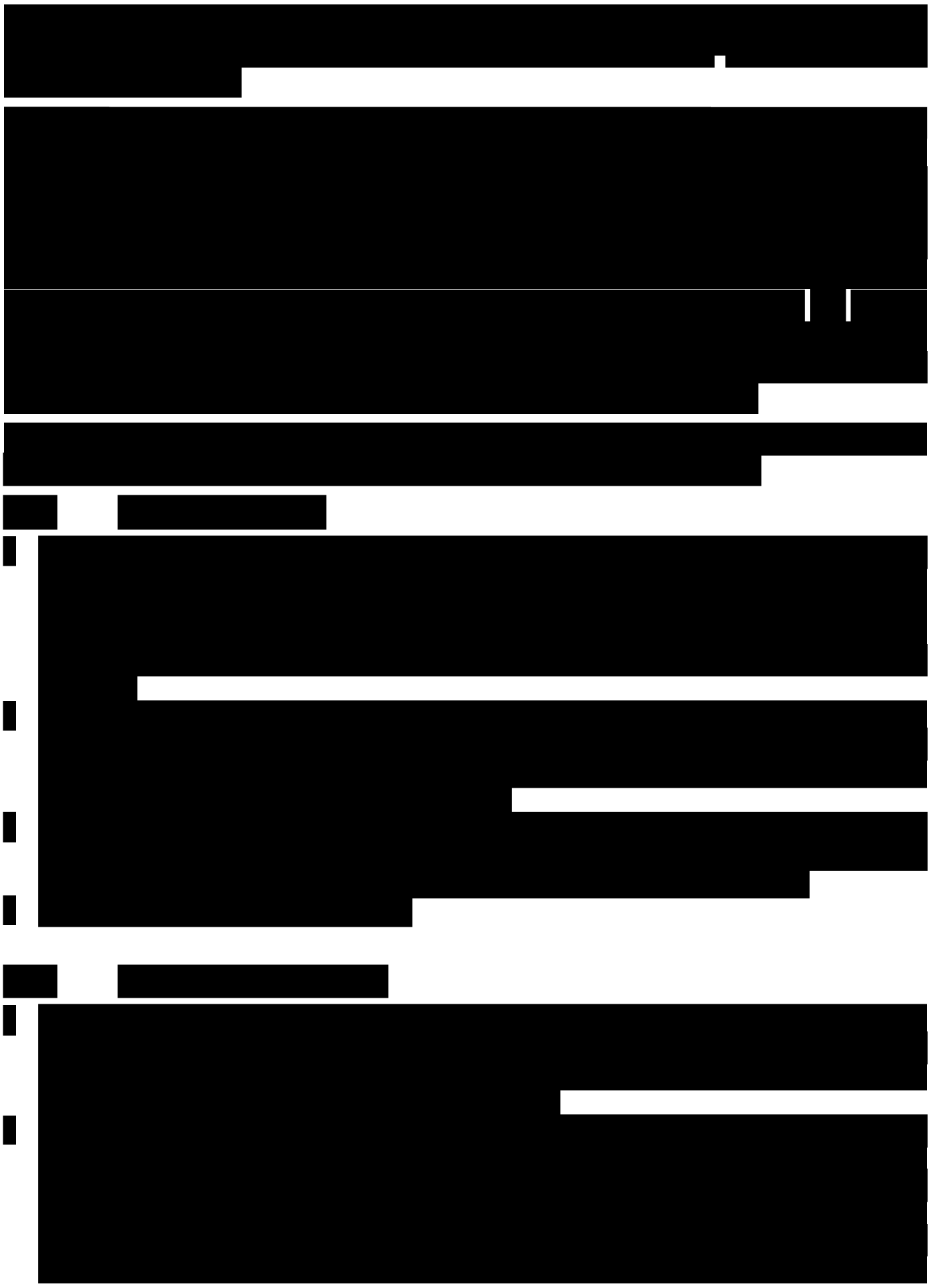
Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The

duration of the washout period is a function of the type of HRT used. The durations of the washout period in the following are suggested guidelines, and investigators should use their judgment in checking serum FSH levels:

- 1 week minimum for vaginal hormonal products (eg, rings, creams, and gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

[redacted]



[redacted]

3.5 Discontinuation of Subjects Following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment and/or participation in the study
- Any clinical AE, laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either psychiatric or physical (eg, infectious disease) illness
- Pregnancy
- Documented disease progression as defined by RECIST (see Appendix 3) unless the subject meets the criteria for treatment beyond progression (Section 3.5.1)
- Clinical deterioration while receiving active study therapy that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Inability to comply with protocol requirements
- Discretion of the investigator
- Protocol-defined reasons for discontinuation (see Section 4.5.6)

In case of pregnancy, the investigator must immediately notify the BMS medical monitor/designee of this event. In the event that a female subject becomes pregnant during a clinical trial, the study drug must be discontinued immediately. Please call the BMS medical monitor within 24 hours of awareness of the pregnancy.

All subjects who discontinue the investigational product should comply with the protocol-specified follow-up procedures outlined in Table 5.1-8. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of a psychiatric or physical illness).

If the study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate CRF page.

3.5.1 Treatment Beyond Disease Progression

As described in Section 1.1.17 accumulating evidence indicates that a minority of subjects with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease. Subjects will be permitted to continue on treatment beyond initial

RECIST v1.1 (see Appendix 3)-defined progressive disease as long as they meet the following criteria:

- Investigator-assessed clinical benefit and without rapid disease progression
- Continue to meet all other study protocol eligibility criteria
- Subject tolerates study drug
- Subject has stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases).
- Subject provides written informed consent prior to receiving any additional BMS-986178, nivolumab, and/or ipilimumab treatment using an ICF describing any reasonably foreseeable risks or discomforts or other alternative treatment options.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor, and an assessment of the risk/benefit of continuing with study therapy must be documented in the study records. Subjects will be re-consented to explain the rationale for this ongoing treatment.

3.5.1.1 Discontinuation due to Further Progression

Subjects should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from the time of initial progression (including all target lesions and new measurable lesions).

The tumor burden volume from the time of initial progression should be used as the reference baseline for comparison with the postprogression assessment.

Any new lesion considered non-measurable at the time of initial progression may become measurable, and therefore, must be included in the tumor burden measurement as follows:

For solid tumors: New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm).

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond the initial investigator-assessed, RECIST v1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

3.5.1.2 Assessment Schedule for Subjects with Post-progression Treatment

Subjects should continue to receive monitoring according to the on-treatment assessments in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, Table 5.1-6, Table 5.1-7, and Table 5.1-8. Radiographic assessment by computed tomography (CT) (preferred) or MRI described in Section 5.1 and Appendix 3 is required when subjects continue post-progression treatment. For subjects that discontinue postprogression treatment with study therapy, no additional radiographic assessments will be required.

3.6 Post-study Drug Follow-up

Post-study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed per the Safety Follow-up (approximately 100 days).

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes, texts, or emails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If the investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

In this study, all drugs will be considered investigational products: BMS-986178, nivolumab, ipilimumab, and tetanus vaccine (Table 4.-1).

Product description and storage information are described in Table 4.-1.

Table 4.-1: Study Drugs for CA012004

Product Description Class and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per label)
BMS-986178 Injection	25 mg/mL (80 mg/vial)	IP	Open	Colorless to pale yellow liquid. Clear to slightly opalescent. Light (few) particulates (consistent in appearance to proteinaceous particulates) may be present.	Store at 2°C to 8°C; do not freeze; protected from light.
Nivolumab Injection	10 mg/mL (100 mg/vial)	IP	Open	Clear to opalescent, colorless to pale yellow liquid. Light (few) particulates may be present.	Store at 2°C to 8°C; store in original package; do not freeze; protected from light.
Ipilimumab Injection	5 mg/mL (200 mg/vial)	IP	Open	Clear, colorless liquid. Light (few) particulates may be present.	Store at 2°C to 8°C; do not freeze; protected from light.
Tetanus vaccine	Per local[a]	IP	Open	Various packaging configuration	Refer to the label on container and/or pharmacy manual

Abbreviations: IP = investigational product

[a] Tetanus vaccine (Tdap preferred, Td or equivalent after discussion with the medical monitor) will be obtained as local commercial product in countries if allowed by local regulations or through investigating sites standard prescribing procedures.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that the investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, the investigational products are BMS-986178, nivolumab, ipilimumab, and tetanus vaccine.

4.2 Non-Investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the SOC for a given diagnosis, may be considered as non-investigational products.

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Nivolumab and ipilimumab will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets). Please refer to Section 9.2.2 for guidance on IP records and documentation.

BMS-986178 Preparation

Calculated dosages for solutions for infusion may be mixed in a D5W bag or normal saline (0.9% NaCl) bag to a recommended concentration. Further details with regard to specific concentrations for drug dilution and administration will be provided in the pharmacy dosing manual for BMS-986178.

BMS-986178 Administration

The administration of the entire bag or syringe (if syringe pump is used) contents should be infused over approximately 30 minutes (including a flush up to 20 mL to completely flush the infusion line), through an IV infusion set (sterile, non-pyrogenic diethylhexyl phthalate [DEHP]-free and non-DEHP free components, low protein binding, polyethersulfone or nylon 0.2-µm in line filter, which will be supplied by the site). Care must be taken to ensure the sterility of the prepared solution, as the drug product does not contain antimicrobial preservatives or bacteriostatic agents. Equilibration to room temperature is recommended for the drug product, infusion fluid, and their combination prior to administration.

Diluted solutions of BMS-986178 for injection are stable for up to 24 hours, at either refrigerated conditions, 2° to 8°C (36° to 46°F), and light protected; 4 hours of which can be under ambient temperature 15 to 25°C (59° to 77°F), and ambient light conditions. The diluted bag should not be shaken. Infusion of BMS-986178 injection must be completed within 24 hours of dilution. The start of drug infusion equals zero (0) hour.

For treatment visits in which both BMS-986178 and nivolumab are administered, nivolumab will be administered first followed by BMS-986178 after a minimum of 30 minutes following completion of the nivolumab infusion and flush. Further details regarding preparation and

administration will be provided separately in site/pharmacy training materials and Investigator's Brochure for BMS-986178.[146]

For treatment visits in which both BMS-986178 and ipilimumab are administered, ipilimumab will be administered first followed by BMS-986178 after a minimum of 30 minutes following completion of the ipilimumab infusion and flush. Further details regarding preparation and administration will be provided separately in site/pharmacy training materials and Investigator's Brochure for BMS-986178.[146]

For treatment visits in which BMS-986178, nivolumab, and ipilimumab are administered, nivolumab will be administered first followed by ipilimumab then BMS-986178. After each 30-minute infusion, there will be a 30-minute waiting period and a flush before starting the next study drug infusion. Further details regarding preparation and administration will be provided separately in site/pharmacy manual and Investigator's Brochure for BMS-986178.[146]

4.4 Method of Assigning Subject Identification

This is an open-label study. All enrolled subjects, including those not dosed, will be assigned sequential subject numbers starting with 00001, (eg, 00001, 00002, 00003... 00010). Those enrolled subjects meeting the inclusion and exclusion criteria will be eligible to be dosed.

Once informed consent has been obtained, the investigator (or designee) will register the subject by an IRT.

The following information is required for registration:

- Gender
- Diagnosis (if applicable)
- Statement that subject is eligible
- Date of informed consent
- Date of Birth

Based on the rate of subject enrollment, the Sponsor will implement an IRT to assign subject numbers, study part and dose level as well as manage drug supply. IRT instructions will be provided to the sites in a separate instruction manual.

Treatment group/dose level will be provided to the site study team through the IRT after the subject has been deemed eligible and is assigned for the study. Site personnel/investigator will receive a receipt confirming the treatment assignment. A copy of this documentation should remain in the subject's chart. Because of the nature of the study design, limited early access to the assignment information will be granted to the study team.

Once it is determined that the subject meets the eligibility criteria, the investigative site will register the subject through IRT prior to the first study drug administration.

Subjects will be assigned to a part or a cohort within a part by IRT. Details about how the subjects will be assigned to a specific part/cohort will be provided in IRT training documentation.

In the dose escalation phases, if a subject discontinues treatment with either BMS-986178, nivolumab, or ipilimumab during the DLT period for reasons other than a DLT, the subject may be replaced with a new subject, if necessary, for safety assessments. Replacement subjects will receive the same treatment but will be assigned a new subject number.

Additional subjects may be added to expansion cohorts and Part 8 if adequate paired pre-treatment and on-treatment biopsy specimens are not obtained from previously assigned subjects. The additional subjects will receive the same treatment as the subjects being replaced, but new subject numbers will be assigned.

Subjects may be permitted to rescreen for the study following agreement between the investigator and the Sponsor/medical monitor.

4.5 Selection and Timing of Dose for Each Subject

Each subject will be assigned to a specific dose level as listed in Section 4.4 during dose escalation. Subjects in the dose expansion will be treated at the MTD, or at the RP2D, as agreed upon by the investigators and the Sponsor.

Nivolumab will be administered as flat doses. There will be no dose escalations or reductions of nivolumab allowed once assigned. There are no premedications recommended for nivolumab on the first cycle. If an acute infusion reaction is noted, the subjects should be managed according to Section 4.5.7.

Ipilimumab will be administered at 1 or 3 mg/kg. There will be no dose escalations or reductions of ipilimumab allowed once assigned. There are no premedications recommended for ipilimumab on the first cycle. If an acute infusion reaction is noted, the subjects should be managed according to Section 4.5.7.

There will be no dose escalations or reductions of BMS-986178 allowed once assigned.

4.5.1 Dose Limiting Toxicity

For the purpose of guiding dose escalation, DLTs will be defined based on the incidence, severity, and duration of AEs, for which no clear alternative cause is identified and that occur within 28 days of initiation of study drug(s). AEs will be graded according to the NCI CTCAE v4.03.

For the purpose of subject management, potential DLTs that occur at any time, whether during dose escalation or dose expansion, will result in all study drug(s) being held pending evaluation of the event's relatedness to study drug, severity, duration, and in accordance with Section 4.5.4. Subjects must meet criteria for treatment prior to re-initiation of study treatment (see Section 4.5.5).

For the purpose of subject management, an AE that meets the DLT criteria, regardless of the cycle in which it occurs, will lead to discontinuation of study drug(s) except for exceptions as outlined in Section 4.5.6. Such subjects will not be retreated with study drug(s) and will enter the Safety Follow-up period of the study.

Subjects who withdraw from the study during the DLT evaluation interval for reasons other than a DLT may be replaced with a new subject at the same dose level. The incidence of DLT(s) during

the DLT evaluation period will be used in dose escalation decisions and to define the MTD. All AEs for which no clear alternative cause is identified occurring after the 28-day DLT period may be considered to represent DLTs for the purposes of defining the RP2D upon agreement between the Sponsor, medical monitor, and investigators, if they are determined to have no clear alternative cause and not related to disease progression. DLT criteria will be utilized for the evaluation of a manageable and tolerable dose in the schedule and dose exploration parts (Parts 4, 5, and 8) and safety cohorts (Parts 6A and 7A).

Any one of the following events for which an alternative cause cannot be identified will be considered a DLT:

A. Hepatic DLT

- Any ≥ Grade 3 elevation of AST, ALT, or total bilirubin
- Grade 2 AST or ALT with symptomatic liver inflammation (eg, right upper quadrant tenderness, jaundice, pruritus)
- AST or ALT > 3 × ULN and concurrent total bilirubin > 2 × ULN without initial findings of cholestasis (elevated serum alkaline phosphatase (eg, findings consistent with Hy's law or FDA definition of potential drug-induced liver injury [pDILI]) (Note that this special category of DLT uses ULN rather than CTC Grade for definition.)

B. Non-hepatic DLT

- Grade 2 or greater uveitis, episcleritis, or iritis
- Any other Grade 2 eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment
- Grade 3 or greater pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction
- Any Grade 3 or greater non-dermatologic, non-hepatic toxicity will be considered a DLT with the following specific EXCEPTIONS:
  - ♦ Grade 3 or Grade 4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 72 hours, and either resolve spontaneously or respond to conventional medical intervention
  - ♦ Grade 3 nausea, vomiting, or diarrhea that lasts less than 72 hours, and either resolves spontaneously or responds to conventional medical intervention
  - ♦ Grade 3 or 4 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
  - ♦ Isolated Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical, or laboratory evidence of impaired end-organ perfusion)
  - ♦ Grade 3 endocrinopathy that is well controlled by hormone replacement
  - ♦ Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor)
  - ♦ Grade 3 fatigue for ≤ 7 days
  - ♦ Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours

C. Dermatologic DLT

- Grade 4 rash

- Grade 3 rash if no improvement (ie, resolution to ≤ Grade 1) after a 1- to 2-week infusion delay. Subjects who have not experienced a Grade 3 skin AE may resume treatment in the presence of Grade 2 skin toxicity.

D. Hematologic DLT

- Grade 4 neutropenia ≥ 7 days in duration
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with clinically significant bleeding, or any requirement for platelet transfusion
- Grade 4 anemia not explained by underlying disease
- Grade ≥ 3 febrile neutropenia
- ≥ Grade 3 hemolysis (ie, requiring transfusion or medical intervention such as steroids)

4.5.2 Management Algorithms for Immuno-Oncology Agents

IO agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab, ipilimumab, and BMS-986178 are considered IO agents in this protocol. Early recognition and management of AEs associated with IO agents may mitigate severe toxicity. Management algorithms have been developed from extensive experience with nivolumab and ipilimumab to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological
- The clinical nature of AEs noted with BMS-986178 will determine the role of the above algorithms for use in toxicities related to its use in this study.

The algorithms recommended for utilization in this protocol are included in Appendix 2.

4.5.3 Guidelines for Dose Modification

Intra-subject dose escalation or reduction of BMS-986178, nivolumab, or ipilimumab is not permitted in this study in order to allow better evaluation of the extended safety and efficacy at individual dose levels and schedules.

4.5.4 Dose Delays due to Toxicity

Subjects who experience the following must have all study drug(s) held:

- Potential DLTs, until DLT relatedness is defined.
- Select AEs and laboratory abnormalities:
  - ≥ Grade 1 pneumonitis
  - ≥ Grade 2 abnormality in AST, ALT, total bilirubin

  - ≥ Grade 2 creatinine
  - ≥ Grade 2 non-skin, drug related AE, with the exception of fatigue
  - ≥ Grade 2 diarrhea or colitis
  - ≥ Grade 2 neurological AE
  - Grade 4 amylase and/or lipase abnormalities regardless of symptoms or clinical manifestation. (Grade 3 amylase or lipase increase that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay)
- AE, laboratory abnormality, or concurrent illness that, in the judgment of the Investigator, warrants delaying the dose of study drug.

If a dose delay is necessary for subjects who are receiving study treatment, all study drugs must be held. Dosing visits are to be delayed but not skipped to ensure that subjects will receive all scheduled treatment cycles if toxicity allows. During treatment, dosing will be as follows:

- Part 2 subjects will receive 12 doses (12 cycles) of q2w BMS-986178 and nivolumab combination therapy.
- Parts 3 and 5 subjects will receive up to 4 doses of q3w BMS-986178 and ipilimumab combination therapy and 4 doses of q3w BMS-986178 monotherapy during maintenance.
- Part 4 subjects will receive 6 doses (6 cycles) of q4w BMS-986178 and nivolumab combination therapy.
- Part 6 subjects will receive 4 doses of q3w BMS-986178, nivolumab, and ipilimumab combination therapy and 3 doses of q4w BMS-986178 and nivolumab during maintenance.
- Part 7 subjects will receive 4 cycles (1 cycle = 6 weeks) of q2w BMS-986178 and nivolumab and q6w ipilimumab combination therapy.
- Part 8
  - Cohorts 1-3 subjects will receive 9 doses of BMS-986178 (q12w) and 27 doses of nivolumab (q4w) combination therapy.
  - Cohort 4 subjects will receive 27 doses of nivolumab (q4w) monotherapy.

Subjects receiving BMS-986178 in combination with nivolumab and/or ipilimumab who have study treatment-related toxicities that meet the criteria for a dose delay should have all study drugs held until the criteria to resume treatment are met (see Section 4.5.5). Subjects who require a dose delay should be re-evaluated weekly, or more frequently if clinically indicated, and resume treatment when criteria are met. Because nivolumab-, ipilimumab- and/or BMS-986178-related AEs require early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, gastrointestinal toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity, and renal toxicity (algorithms are provided in Appendix 2).

For subjects who have dose delays, the total study treatment period should not exceed 36 weeks, unless approved by the BMS Medical Monitor (or designee). Extensions to the period of dose delays may be granted for individual subjects on a case by case basis after specific consultation and agreement between the investigator and BMS medical monitor in settings where risk/benefit may justify continued study therapy (eg, subject deriving clinical benefit who requires prolonged

steroid taper for the management of non-DLT drug-related AEs, or experiences delays for the management of a non-drug-related AE).

The end of cycle tumor assessments (ie, CT/MRI, etc) will continue every 8 weeks Part 1-7 or every 12 weeks Part 8 (± 1 week) relative to the subject's first dose of BMS-986178, regardless of any treatment delay incurred.

4.5.5 Criteria to Resume Treatment

4.5.5.1 Criteria to Resume Treatment in Subjects with a Dose Delay

If a dose delay is necessary for subjects who are receiving study treatment, all study drugs must be held.

Subsequent dosing with study therapy may resume once non-DLT AEs resolve to Grade 1 or baseline.

Subjects experiencing AEs not meeting the criteria for permanent discontinuation as outlined in Section 4.5.6 may resume treatment with study medication under the following criteria:

- Subjects may resume treatment with study drug when the AE(s) resolve to Grade ≤ 1 or baseline value with the following exceptions:
  - Subjects may resume treatment in the presence of Grade 2 fatigue.
  - Subjects who have not experienced a Grade 3 skin AE may resume treatment in the presence of Grade 2 skin toxicity.
  - Subjects with Grade 2 eye pain or blurred vision not meeting DLT criteria (Section 4.5.1) must resolve to baseline prior to resuming study therapy.
  - Any pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for resumption of treatment if discussed with and approved by BMS Medical Monitor (or designee).
  - Subjects with endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor (or designee). Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - For subjects with Grade 2 AST, ALT and/or total bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
  - Subjects with a Grade 4 amylase or lipase increase that is not associated with symptoms or clinical manifestations of pancreatitis can be restarted on therapy once the levels have decreased to Grade 3 or lesser - and after consultation with the BMS Medical Monitor.
- If study treatment is delayed past the scheduled dosing visit per protocol, the scheduled study treatment administration will be delayed, but not skipped, until dosing resumes to ensure that subjects will receive all scheduled treatment cycles if toxicity allows.
- The consideration to re-initiate study therapy under these exceptions will be made on a case by case basis after considering the overall risk/benefit profile and in consultation between the

investigator and the study Sponsor. Any AE with clinical risk will be assessed on a case by case basis with the investigator and the BMS Medical Monitor to determine the risks and benefits of continuing on therapy following resolution versus discontinuing therapy permanently.

- If dosing is delayed ≥ 9 weeks, the subject must be permanently discontinued from study treatment, except as specified in Section 4.5.6. Extensions to the period of dose delays may be granted for individual subjects on a case by case basis after specific consultation and agreement between the investigator and BMS medical monitor in settings where risk/benefit may justify continued study therapy (eg, subject deriving clinical benefit who requires prolonged steroid taper for the management of non-DLT immune-related AEs, or experiences delays for management of a non-drug-related AE).
- Dosing delays to allow prolonged steroid tapers to manage AEs are allowed. Additionally, dosing delays ≥ 9 weeks (as noted above) that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor.
- If the toxicity resolves to ≤ Grade 1 or baseline > 9 weeks after the last dose, the subject does not meet the criteria for permanent discontinuation (see Section 4.5.6), and the investigator believes that the subject is deriving clinical benefit, the subject may be eligible to resume study treatment(s) following approval from the BMS Medical Monitor (or designee).
- Tumor assessments should continue as per protocol even if dosing is delayed.

4.5.5.2 Criteria for Resuming Treatment in Subjects with an Infusion Reaction

In subjects experiencing an infusion reaction with study drug administration, the following guidelines for dose delay and criteria to resume treatment are to be followed:

- Parts 2, 4, 6, 7, and 8 on days with administration of BMS-986178 and nivolumab only: If a nivolumab-related infusion reaction prevents subsequent infusion of BMS-986178 on the same day, the dose of BMS-986178 should be replaced as soon as possible. In such instances, at least 12 days must elapse between the replacement dose of BMS-986178 and the administration of the next dose of nivolumab combined with BMS-986178.
- Parts 3 and 5: If an ipilimumab-related infusion reaction prevents subsequent infusion of BMS-986178 on the same day, the dose of BMS-986178 should be replaced as soon as possible. In such instances, at least 19 days must elapse between the replacement dose of BMS-986178 and the administration of the next dose of ipilimumab combined with BMS-986178 on a q3w schedule.
- Parts 6 or 7: If a nivolumab-related infusion reaction prevents subsequent infusion of ipilimumab and/or BMS-986178 on the same day, the dose of ipilimumab and BMS-986178 should be replaced as soon as possible. In such instances, at least 19 days must elapse between the replacement dose of ipilimumab and the administration of the next dose of BMS-986178 and nivolumab combined with ipilimumab on a q3w schedule. However, if an ipilimumab-related infusion reaction prevents subsequent infusion of BMS-986178 on the same day, the dose of BMS-986178 should be replaced as soon as possible. In such instances, at least 19 days must elapse between the replacement dose of BMS-986178 and the administration of the next dose of BMS-986178 and nivolumab combined with ipilimumab.

Guidelines for management of an infusion reaction during study drug administration are included in Section 4.5.7.

4.5.6 Guidelines for Permanent Discontinuation

Subjects will be required to permanently discontinue all study drugs for the following AEs:

- Progressive Disease (see also Section 3.5.1 for details regarding continuing treatment beyond disease progression)
- Clinical deterioration, as assessed by the investigator
- Grade 3 infusion reaction that does not return to Grade 1 in less than 6 hours
- Grade 3 or greater pneumonitis, bronchospasm or, neurologic toxicity
- Life-threatening skin toxicity (toxic epidermal necrolysis)
- Grade 2 or greater episcleritis, or iritis. Any Grade 2 or greater drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- Any Grade 4 AE; however, an exception may be made for the following upon consultation between the investigator and BMS medical monitor:
  - Grade 4 electrolyte abnormalities ≤ 72 hours in duration
  - Grade 4 neutropenia ≤ 7 days in duration
  - Grade 4 lymphopenia or leukopenia.
  - Grade 4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any toxicity that meets DLT criteria as defined in Section 4.5.1; however, an exception may be made on a case-by-case basis upon consultation between the investigator and BMS medical monitor:
  - Grade 3 diarrhea, nausea, vomiting, or abdominal pain that returns to Grade 1 or baseline within 3 days with medical intervention
  - AST or ALT > 5× and < 8× institutional ULN for < 2 weeks
  - Grade 3 pruritus or rash that returns to Grade 1 or baseline within 7 days with medical intervention

    The consideration to re-initiate study therapy under these exceptions will be made on a case-by-case basis after considering the overall risk/benefit profile and in consultation between the investigator and the Sponsor.
- Confirmed CR

- Completion of 24 weeks of treatment (Parts 1-7) or 24 months for Part 8. Subjects in Part 2, 4 6, or 7 that continue for additional cycles up to 24 months of treatment.

All subjects who discontinue study drug(s) should comply with protocol-specified follow-up procedures as outlined in Section 5.1. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (eg, is imprisoned or involuntarily incarcerated for the treatment of a psychiatric or physical illness).

If study treatment is discontinued prior to the subject's completion of treatment, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate CRF page.

4.5.7 Treatment of Drug-Related Infusion Reactions

Since BMS-986178, nivolumab, and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion reactions. However, if an infusion reaction or a hypersensitivity reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE v4.03 guidelines and reported on the appropriate CRF.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: Mild reaction; infusion interruption not indicated; intervention not indicated.

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg, to be given at least 30 minutes before additional study drug administrations.

For Grade 2 symptoms: Moderate reaction; requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours.

- Stop the drug being infused (either BMS-986178, nivolumab, or ipilimumab infusion), begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); monitor subject until resolution of symptoms.
- Bronchodilator or corticosteroid therapy may also be administered as appropriate.
- The infusion may be restarted at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely.

- The amount of study drug infused must be recorded on the CRF.
- If symptoms recur, then no further dosing with the relevant drug and/or subsequent drug, as the case may be, will be administered at that visit.
- The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional BMS-986178, nivolumab, or ipilimumab administrations (whichever caused the reaction). If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

Late-occurring Symptoms:

In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

For Grade 3 or Grade 4 symptoms: Severe reaction; Grade 3: prolonged [eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated.

Immediately discontinue study drug infusion. Begin an IV infusion of normal saline and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 0.5 mg (1:1,000 solution) for subcutaneous administration or 0.1 to 0.25 mg (1:10,000 solution) injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug(s) will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Study drug will be administered in the clinical facility by trained medical personnel. The investigator and the study personnel will ensure that each subject receives the prescribed dose of study drug. Treatment compliance will be monitored by drug accountability as well as by recording BMS-986178, nivolumab, and/or ipilimumab administration in subjects' medical records and CRFs.

Drug supplies will be inventoried and accounted for throughout the study. The Drug Accountability Log will be reviewed by the study monitor during site visits and at the completion of the study. Any discrepancy should be brought to the attention of the Sponsor.

4.8 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials, and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS study monitor unless study drug containers must be immediately destroyed as required for safety or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures (SOPs) and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, (ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the monitor to review throughout the clinical trial period.

If conditions for on-site destruction cannot be met, the responsible BMS study monitor will make arrangements for the return of study drug to the Sponsor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible study monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.10 Retained Samples for Bioavailability/Bioequivalence

Not Applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures are presented in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, Table 5.1-6, Table 5.1-7, and Table 5.1-8. In limited instances, scheduled events can occur outside of the indicated timeframes; BMS should be notified of these instances.

Table 5.1-1: Screening Procedural Outline (CA012004) - Parts 1 - 8

Procedure	Screening Visit (-28 day to -1 Visit)	D -14 to -1 Visit	Notes
Eligibility Assessments			
Informed Consent	X		A subject is considered enrolled only when a protocol-specific informed consent is signed.
Inclusion/Exclusion Criteria	X		
Medical History	X		Include any toxicities or allergy related to previous treatments.
Prior Cancer Therapies	X		
ECOG Performance	X		See Appendix 4.
Archived Tumor Tissue Sample	X		An archival, FFPE tumor tissue block, or slide samples (a minimum of 15 unstained slides [25 preferred]), may be provided by all subjects. Samples should be shipped to the central laboratory.
Fresh Pre-treatment Tumor Biopsy	X		**All subjects require a mandatory pre- and on-treatment biopsy.** **Archival specimens may not be substituted for fresh baseline specimens but can be submitted to help understand the evolution of the tumor (ie, PD-L1 expression changes over time).**
Blood PD, Blood Genotype, and Blood TCR	X		
Safety Assessments			
Physical Examination (PE)	X		If the screening PE is performed within 24 hours prior to dosing on D1, then a single exam may count as both the screening and predose evaluations.
Physical Measurements	X		Includes height and weight.
Vital Signs	X		Includes body temperature, respiratory rate, seated blood pressure, and heart rate.
Oxygen Saturation	X		Pulse oximetry collected at rest.
Electrocardiogram (ECGs)	X		ECGs should be recorded after the subject has been supine for at least 5 minutes.

Table 5.1-1: Screening Procedural Outline (CA012004) - Parts 1 - 8

Procedure	Screening Visit (-28 day to -1 Visit)	D -14 to -1 Visit	Notes
			All ECG tests should be performed as a single measurement.
Laboratory Tests	Laboratory tests listed below must be completed within 2 weeks of D1 unless otherwise noted.		
Serology	X		Within 28 days of dosing, if required: Hep B surface antigen, and Hep C antibody (if Hep C antibody is positive reflex to Hep C RNA), or Hep C RNA. **Note**: Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements.
Chemistry (Excluding LFTs)		X	See Section 5.3.2. Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, carbon dioxide, phosphorus, BUN, creatinine, creatinine clearance, fasting glucose, total protein, albumin, amylase, lipase, uric acid, ferritin, CRP, and LDH.
CBC with Differential and Platelets		X	
LFT Assessment		X	See Section 5.3.2.
Urinalysis		X	See Section 5.3.2.
Thyroid Function Tests (TFTs)		X	TSH with free T3 and free T4.
Genetic Mutations	X		See Section 5.7. Collected as part of the medical history on appropriate CRF
Tumor Markers (Serum)	X		CA125, AFP, CEA, CA19-9, and PSA for all subjects
Pregnancy Test		X	For WOCBP only; serum will be collected at **screening and within 24 hours prior to dosing**. The serum pregnancy test may be completed on the first day of treatment, provided the results are available before the start of study therapy. If performed within 24 hours of dosing on C1D1, then C1D1 pregnancy test is not required.
Follicle Stimulating Hormone (FSH)	X		If needed to document post-menopausal status as defined in Section 3.3.3.
[redacted]		[redacted]	[redacted].

Table 5.1-1: Screening Procedural Outline (CA012004) - Parts 1 - 8

Procedure	Screening Visit (-28 day to -1 Visit)	D -14 to -1 Visit	Notes
Adverse Event Reporting			
Clinical Complaints		X	Collected during the 2 weeks prior to C1D1.
Monitor for Serious Adverse Events	X		All SAEs must be collected from the date of the subject's written consent until 100 days of discontinuation of dosing. SAEs should be approved in eCRF directly within 5 business days of entry.
Efficacy Assessments			
Tumor Assessments	X		CT with contrast is the preferred modality (MRI if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum and should include other anatomic regions as indicated by individual subject disease histories.
Brain Imaging	X		Brain imaging (CT/MRI) for subjects with history or symptoms of brain metastases and who have not had brain imaging within 30 days of anticipated first study drug administration.
Bone Scan	X		As clinically indicated (eg, subjects with history or symptoms of bone metastases), but bone scans will not be considered a modality for the assessment for measurable disease.
IRT Subject Assignment/ Treatment Assignment	X	X	After the subject consents, the sites will use the IRT to have the subject number assigned. After the subject has completed all screening procedures, IRT will be used for treatment assignment or discontinuing the subject. Subsequent visits will need to be registered into the IRT system for drug supply.

Abbreviations: AFP = alpha fetal protein; BUN = blood urea nitrogen; C = Cycle; CEA = carcinoembryonic antigen; CBC = complete blood count; CRC = colorectal cancer; CRF = case report form; CRP = C-reactive protein; CT = computed tomography; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed, paraffin-embedded; HIV = human immunodeficiency virus; HPV = Human papillomavirus; IRT = Interactive Response Technology; LDH = lactic acid dehydrogenase; LFT =liver function test; MSI = microsatellite instability; MRI = magnetic resonance imaging; PD = pharmacodynamic; PSA = Prostate-Specific Antigen; RNA = ribonucleic acid; T3 =triiodothyronine; T4 = thyroxine; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; WOCBP = women of child bearing potential.

Table 5.1-2: On Treatment Procedural Outline Parts 1 and 2 (CA012004 - q2w Dosing)

(C1-C12, Additional Cycles) Cycle = 2 Weeks	C1			C2-C8	C9	C10 - beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Safety Assessments								
Physical Examination (PE)	X						X	Predose (C1 only); See note in screening.
Symptom-directed PE		X	X	X	X	X		To include signs and symptoms
Physical Measurements	X			X	X	X		Weight only
Vital Signs	X	X		X	X	X	X	See note in screening.[e] Observe subjects 4 hours post-infusion C1D1 and C2D1
12-Lead Electrocardiogram (ECG)	X				X			All ECG tests should be performed as a single measurement. ECGs will be done at both predose and 4 hours when BMS-986178 PK sample is collected (ECGs should be done prior to the PK sample) at C1D1 and C9D1.
Laboratory Tests	See note in screening procedures and Section 5.3.2. Predose on D1.							
Chemistry (Excluding LFTs)	X	X	X	X	X	X	X	**Collect on C1D1, C1D2 and C1D8 and every cycle D1**
CBC with Differential and Platelets	X	X	X	X	X	X	X	
LFT Assessment	X	X	X	X	X	X	X	AST, ALT, ALP, and T. Bilirubin. Direct Bilirubin (only if T. Bilirubin is elevated);

Table 5.1-2: On Treatment Procedural Outline Parts 1 and 2 (CA012004 - q2w Dosing)

(C1-C12, Additional Cycles) Cycle = 2 Weeks	C1			C2-C8	C9	C10 - beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
								GGT (if ALP increase is clinically significant)
Thyroid Test	X			X	X	X	X	TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration. **Every odd cycle D1**
Tumor Markers	X			X	X	X	X	eg, CA125, AFP, CEA, CA19-9, and PSA for subjects with qualifying tumors **Every odd cycle D1**
Urinalysis	As clinically indicated. See Section 5.3.2.							
Pregnancy Test[f]	X			X	X	X	X	
Adverse Event (AE) Reporting								
[redacted]	[redacted]							
Monitor for Non-Serious Adverse Events	Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.							
Monitor for Serious Adverse Events	See note in screening procedures (Table 5.1-1).							

Table 5.1-2: On Treatment Procedural Outline Parts 1 and 2 (CA012004 - q2w Dosing)

(C1-C12, Additional Cycles) Cycle = 2 Weeks	C1			C2-C8	C9	C10 - beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Pharmacokinetic Assessments	See Table 5.5.1-1 for specific samples at each cycle during the study							
Serial Serum PK Sampling for BMS-986178	See Table 5.5.1-1 for specific samples at each cycle during the study.							
BMS-986178 ADA Sample	See Table 5.5.1-1 for specific samples at each cycle during the study							
Serial Serum PK Sampling for Nivolumab (Part 2 Only)	See Table 5.5.1-1 for specific samples at each cycle during the study							
Nivolumab ADA Sample (Part 2 Only)	See Table 5.5.1-1 for specific samples at each cycle during the study							
Biomarker Assessments	See Table 5.6-1 for specific samples at each cycle during the study.							
Blood RNA, Blood RO	See Table 5.6-1 for specific samples at each cycle during the study.							
Blood PD	See Table 5.6-1 for specific samples at each cycle during the study.							
PBMC	See Table 5.6-1 for specific samples at each cycle during the study.							
Blood Multiparameter Flow	See Table 5.6-1 for specific samples at each cycle during the study.							
Serum Factors	See Table 5.6-1 for specific samples at each cycle during the study.							
PD Plasma	See Table 5.6-1 for specific samples at each cycle during the study.							

Table 5.1-2: On Treatment Procedural Outline Parts 1 and 2 (CA012004 - q2w Dosing)

(C1-C12, Additional Cycles) Cycle = 2 Weeks	C1			C2-C8	C9	C10 - beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Mandatory Fresh Tumor Biopsy	See Table 5.6-1 for specific samples at each cycle during the study.							
Blood TCR	See Table 5.6-1 for specific samples at each cycle during the study.							
Efficacy Assessments								
Tumor Assessments	Every 8 weeks (± 1 week)						X	By methods used at baseline. Same modality should be used for all assessments. Assessed by RECIST v1.1; see Appendix 3. Assessment to be performed prior to initiating next cycle of treatment. An unconfirmed PR or unconfirmed CR must be confirmed at least 4 weeks after initial assessment.
Brain Imaging	As clinically indicated							
Bone Scan	As clinically indicated							
Clinical Drug Supplies								
Parts 1 and 2 BMS-986178	X			X	X	X		Supplied by BMS Use vials assigned per IRT
Part 2 **ONLY** Nivolumab (240 mg Flat Dose)	X			X	X	X		Supplied by BMS Use vials assigned per IRT

Abbreviations: ADA = anti-drug antibody; AFP = alpha fetal protein; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BMS = Bristol-Myers Squibb; C = Cycle; CBC = complete blood count; CEA = carcinoembryonic antigen; CR = complete response; CRC = colorectal cancer; D = Day; EOT = end of treatment; LFT = liver function test; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IRT = Interactive Response Technology; LFT = liver function test; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PR = partial response; PSA

= Prostate-Specific Antigen; RNA = ribonucleic acid; RO = receptor occupancy; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; VS = vital signs.

[a] EOT is defined as the visit where the decision is made to discontinue the subject from treatment.

[b] For subjects who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C12D14) and the start of the Week 1 Safety Follow-up visit.

[c] For subjects who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated and will be considered the start of the Week 1 Safety Follow-up visit.

[d] Subjects will have procedures listed in this table completed at all cycles. For these treatment groups, 1 cycle = 2 weeks, up to 12 cycles of dosing. Subjects who have additional cycles will follow this same time and events table.

[e] For BMS-986178, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion except for C1D1 and C2D1 (where vital signs will be obtained every 30 minutes until 4 hours post infusion). For nivolumab, vital signs will be obtained before the infusion and then every 30 minutes (± 10 minutes) until the start of BMS-986178 infusion or per institution guidelines for administration of nivolumab. The 30-minute post nivolumab infusion VS may correspond to the pre-infusion BMS-986178 VS. In the event BMS-986178 administration is delayed, nivolumab vital signs will be obtained until 60 minutes after completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.

[f] Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If the pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue and immediately notify the BMS Medical Monitor/designee per Section 6.4.

Table 5.1-3: On Treatment Procedural Outline Parts 3 and 5 (CA012004 - q3w Dosing)

(C1-C8, Additional Cycles) Cycle = 3 weeks	C1				C2-C3	C4	C5-beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Safety Assessments									
Physical Examination (PE)	X							X	Predose (C1 Only) See note in screening
Symptom-directed PE		X	X	X	X	X	X		To include signs and symptoms
Physical Measurements	X				X	X	X		Weight only
Vital Signs	X	X			X	X	X	X	See note in screening.[e] Observe subjects 4 hours post-infusion C1D1 and C2D1
12-Lead Electrocardiogram (ECGs)	X					X			All ECG tests should be performed as a single measurement. ECGs will be done at both predose and 4 hours when BMS-986178 PK sample is collected (ECGs should be done prior to the PK sample) at C1D1 and C4D1.
Laboratory Tests	See note in screening procedures and Section 5.3.2. Predose on D1.								
Chemistry (Excluding LFTs)	X	X	X	X	X	X	X	X	Collect on C1D1, C1D2, C1D8, and C1D15, and every cycle D1
CBC with Differential and Platelets	X	X	X	X	X	X	X	X	
LFT Assessment	X	X	X	X	X	X	X	X	AST, ALT, ALP, and T. Bilirubin. Direct Bilirubin (only if T. Bilirubin is elevated);

Table 5.1-3: On Treatment Procedural Outline Parts 3 and 5 (CA012004 - q3w Dosing)

(C1-C8, Additional Cycles) Cycle = 3 weeks	C1				C2-C3	C4	C5-beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
									GGT (if ALP increase is clinically significant
Thyroid Test	X				X		X	X	To include TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration. **Every odd cycle D1**
Tumor Markers	X				X	X	X	X	eg, CA125, AFP, CEA, CA19-9, and PSA for subjects with qualifying tumors **Every odd cycle D1**
Urinalysis	As clinically indicated. See Section 5.3.2 .								
Pregnancy Test[f]	X				X	X	X	X	
Adverse Event Reporting									
[redacted]	[redacted]								
Monitor for Non-Serious Adverse Events	Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.								
Monitor for Serious Adverse Events	See note in screening procedures (Table 5.1-1).								

Table 5.1-3: On Treatment Procedural Outline Parts 3 and 5 (CA012004 - q3w Dosing)

(C1-C8, Additional Cycles) Cycle = 3 weeks	C1				C2-C3	C4	C5-beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Pharmacokinetic Assessments	See Table 5.5.1-3								
Serial Serum PK Sampling BMS-986178	Refer to Table 5.5.1-3.								
BMS-986178 ADA Sampling	Refer to Table 5.5.1-3.								
Serial Serum PK Sampling for Ipilimumab	Refer to Table 5.5.1-3.								
Ipilimumab ADA sampling	Refer to Table 5.5.1-3.								
Biomarker Assessments	See Table 5.6-2 for specific samples at each cycle during the study.								
Blood RNA, Blood RO	See Table 5.6-2 for specific samples at each cycle during the study.								
Blood PD	See Table 5.6-2 for specific samples at each cycle during the study.								
PBMC	See Table 5.6-2 for specific samples at each cycle during the study.								
Blood Multiparameter Flow	See Table 5.6-2 for specific samples at each cycle during the study.								
Serum Factors	See Table 5.6-2 for specific samples at each cycle during the study.								
PD Plasma	See Table 5.6-2 for specific samples at each cycle during the study.								

Table 5.1-3: On Treatment Procedural Outline Parts 3 and 5 (CA012004 - q3w Dosing)

(C1-C8, Additional Cycles) Cycle = 3 weeks	C1				C2-C3	C4	C5-beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Mandatory Fresh Tumor Biopsy	See Table 5.6-2 for specific samples at each cycle during the study.								
Blood TCR	See Table 5.6-2 for specific samples at each cycle during the study.								
Efficacy Assessments									
Tumor Assessments	Every 8 weeks (± 1 week) Note: If subject completes 24 weeks of dosing, C8D21 will be the last cycle visit (EOT), this will be at Week 25, and the 27-week scan should be done at this time.							X	By methods used at baseline. Same modality should be used for all assessments. Assessed by RECIST v1.1; see Appendix 3. Assessment to be performed prior to initiating next cycle of treatment. An unconfirmed PR or unconfirmed CR must be confirmed at least 4 weeks after initial assessment.
Brain Imaging	As clinically indicated								
Bone Scan	As clinically indicated								
Clinical Drug Supplies									
BMS-986178	X				X	X	X		All subjects Supplied by BMS Use vials assigned per IRT
Part 3 Ipilimumab (1 mg/kg)	X				X	X			Supplied by BMS Use vials assigned per IRT

Table 5.1-3: On Treatment Procedural Outline Parts 3 and 5 (CA012004 - q3w Dosing)

(C1-C8, Additional Cycles) Cycle = 3 weeks	C1				C2-C3	C4	C5-beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Part 5 Ipilimumab (3 mg/kg)	X				X	X			Supplied by BMS Use vials assigned per IRT

Abbreviations: ADA = anti-drug antibody; AFP = alpha fetal protein; BMS = Bristol-Myers Squibb; C=Cycle; CBC = complete blood count; CEA = carcinoembryonic antigen; CR = complete response; CRC = colorectal cancer; D = Day; ECG = electrocardiogram; EOT = end of treatment; LFT = liver function test; IRT = Interactive Response Technology; LFT = liver function test; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PR = partial response; PSA = Prostate-Specific Antigen; RNA = ribonucleic acid; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; VS = vital signs.

[a] EOT is defined as the visit where the decision is made to discontinue the subject from treatment.

[b] For subjects who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C8D21) and the start of the Week 1 Safety Follow-up visit.

[c] For subjects who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated and will be considered the start of the Week 1 Safety Follow-up visit.

[d] Subjects will have procedures listed in this table completed at all cycles. For these treatment groups 1 cycle = 3 weeks, up to 8 cycles of dosing. Subjects who have additional cycles will follow this same time and events table.

[e] For BMS-986178, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion except for C1D1 and C2D1 (where vital signs will be obtained every 30 minutes until 4 hours post infusion). Vital signs will be obtained before the infusion and then every 30 minutes (± 10 minutes) until the start of BMS-986178 infusion or per institution guidelines for administration of ipilimumab. The 30-minute post ipilimumab infusion VS may correspond to the pre-infusion BMS-986178 VS. In the event BMS-986178 administration is delayed, ipilimumab vital signs will be obtained until 60 minutes after completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.

[f] Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If the pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue and immediately notify the BMS Medical Monitor/designee per Section 6.4.

Table 5.1-4: On Treatment Procedural Outline Part 4 (CA012004 - q4w Dosing)

(C1-C6, Additional Cycles) Cycle = 4 weeks	C1				C2-C4		C5	C6-beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Safety Assessments										
Physical Examination (PE)	X								X	Predose (C1 only). See note in screening.
Symptom-directed PE		X	X	X	X	X	X	X		To include signs and symptoms
Physical Measurements	X				X		X	X		Weight only
Vital Signs	X	X			X		X	X	X	See note in screening.[e] Observe subjects 4 hours post-infusion C1D1 and C2D1
12-Lead Electrocardiogram (ECGs)	X						X			All ECG tests should be performed as a single measurement. ECGs will be done at both predose and 4 hours when BMS-986178 PK sample is collected (ECGs should be done prior to the PK sample) at C1D1 and C5D1.
Laboratory Tests	See note in screening procedures and Section 5.3.2. Predose on D1.									
Chemistry (Excluding LFTs)	X	X	X	X	X	X	X	X	X	
CBC with Differential and Platelets	X	X	X	X	X	X	X	X	X	
LFT Assessment	X	X	X	X	X	X	X	X	X	AST, ALT, ALP, and T. Bilirubin. Direct Bilirubin (only if T. Bilirubin is elevated); GGT (if ALP increase is clinically significant)

Table 5.1-4: On Treatment Procedural Outline Part 4 (CA012004 - q4w Dosing)

(C1-C6, Additional Cycles) Cycle = 4 weeks	C1				C2-C4		C5	C6-beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Thyroid Test	X				X		X	X	X	TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Tumor Markers	X				X		X	X	X	eg, CA125, AFP, CEA, CA19-9, and PSA for subjects with qualifying tumors **Every odd cycle D1**
Urinalysis	As clinically indicated. See Section 5.3.2									
Pregnancy Test[f]	X				X		X	X	X	
Adverse Event Reporting										
[redacted]	[redacted]									
Monitor for Non-Serious Adverse Events	Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.									
Monitor for Serious Adverse Events	See note in screening procedures (Table 5.1-1).									
Pharmacokinetic Assessments	See Table 5.5.1-2 for specific samples at each cycle during the study.									
Serial Serum PK Sampling BMS-986178	See Table 5.5.1-2 for specific samples at each cycle during the study.									

Table 5.1-4: On Treatment Procedural Outline Part 4 (CA012004 - q4w Dosing)

(C1-C6, Additional Cycles) Cycle = 4 weeks	**C1**				**C2-C4**		**C5**	**C6-beyond**		**Window (± 2 days)**
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
BMS-986178 ADA Sample	See Table 5.5.1-2 for specific samples at each cycle during the study.									
Serial Serum PK Sampling for Nivolumab	See Table 5.5.1-2 for specific samples at each cycle during the study.									
Nivolumab ADA Sampling	See Table 5.5.1-2 for specific samples at each cycle during the study.									
Biomarker Assessments	See Table 5.6-3 for specific samples at each cycle during the study.									
Blood RNA, Blood RO	See Table 5.6-3 for specific samples at each cycle during the study.									
Blood PD	See Table 5.6-3 for specific samples at each cycle during the study.									
PBMC	See Table 5.6-3 for specific samples at each cycle during the study.									
Blood Multiparameter Flow	See Table 5.6-3 for specific samples at each cycle during the study.									
Serum Factors	See Table 5.6-3 for specific samples at each cycle during the study.									
PD Plasma	See Table 5.6-3 for specific samples at each cycle during the study.									
Mandatory Fresh Tumor Biopsy	See Table 5.6-3 for specific samples at each cycle during the study.									
Blood TCR	See Table 5.6-3 for specific samples at each cycle during the study.									
Efficacy Assessments										

Table 5.1-4: On Treatment Procedural Outline Part 4 (CA012004 - q4w Dosing)

(C1-C6, Additional Cycles) Cycle = 4 weeks	C1				C2-C4		C5	C6-beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Tumor Assessments	Every 8 weeks (± 1 week)								X	By methods used at baseline. Same modality should be used for all assessments. Assessed by RECIST v1.1; see Appendix 3. Assessment to be performed prior to initiating next cycle of treatment. An unconfirmed PR or unconfirmed CR must be confirmed at least 4 weeks after initial assessment.
Brain Imaging	As clinically indicated									
Bone Scan	As clinically indicated									
Clinical Drug Supplies										
BMS-986178	X				X		X	X		Supplied by BMS Use vials assigned per IRT
Nivolumab	X				X		X	X		Supplied by BMS Use vials assigned per IRT

Abbreviations: ADA = anti-drug antibody; AFP = alpha fetal protein; BMS = Bristol-Myers Squibb; C = Cycle; CBC = complete blood count; CEA = carcinoembryonic antigen; CR = complete response; CRC = colorectal cancer; D = Day; EOT = end of treatment; LFT = liver function test; IRT = Interactive Response Technology; LFT = liver function test; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PR = partial response; PSA = Prostate-Specific Antigen; RNA = ribonucleic acid; RO = receptor occupancy; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; VS = vital signs.

[a] EOT is defined as the visit where the decision is made to discontinue the subject from treatment.

[b] For subjects who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C6D28) and the start of the Week 1 Safety Follow-up visit.

[c] For subjects who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated and will be considered the start of the Week 1 Safety Follow-up visit.

[d] Subjects will have procedures listed in this table completed at all cycles. For these treatment groups 1 cycle = 4 weeks, up to 6 cycles of dosing. Subjects who have additional cycles will follow this same time and events table.

[e] For BMS-986178, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion except for C1D1 and C2D1 (where vital signs will be obtained every 30 minutes until 4 hours post infusion). For nivolumab, vital signs will be obtained before the infusion and then every 30 minutes (± 10 minutes) until the start of BMS-986178 infusion or per institution guidelines for administration of nivolumab. The 30-minute post nivolumab infusion VS may correspond to the pre-infusion BMS-986178 VS. In the event BMS-986178 administration is delayed, nivolumab vital signs will be obtained until 60 minutes after completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.

[f] Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If the pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue and immediately notify the BMS Medical Monitor/designee per Section 6.4.

Table 5.1-5: On Treatment Procedural Outline Part 6 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with RCC)

(C1-C7, Additional Cycles) Cycle = 3 weeks for C1-C4 Cycle = 4 weeks for C5 and beyond	C1				C2-C3	C4	C5-Beyond			Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**D15**	**EOT[a,b,c]**	**Notes[d]**
Safety Assessments										
Physical Examination (PE)	X								X	Predose (C1 Only) See note in screening
Symptom-directed PE		X	X	X	X	X	X	X		To include signs and symptoms
Physical Measurements	X				X	X	X			Weight only
Vital Signs	X	X			X	X	X		X	See note in screening.[e] Observe subjects 4 hours post-infusion C1D1 and C2D1
12-Lead Electrocardiogram (ECGs)	X					X				All ECG tests should be performed as a single measurement. ECGs will be done at both predose and 4 hours when BMS-986178 PK sample is collected (ECGs should be done prior to the PK sample) on C1D1 and C4D1.
Laboratory Tests	See note in screening procedures and Section 5.3.2. Predose on D1.									
Chemistry (Excluding LFTs)	X	X	X	X	X	X	X	X	X	

Table 5.1-5: On Treatment Procedural Outline Part 6 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with RCC)

(C1-C7, Additional Cycles) Cycle = 3 weeks for C1-C4 Cycle = 4 weeks for C5 and beyond	C1				C2-C3	C4	C5-Beyond			Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**D15**	**EOT[a,b,c]**	**Notes[d]**
CBC with Differential and Platelets	X	X	X	X	X	X	X	X	X	
LFT Assessment	X	X	X	X	X	X	X	X	X	AST, ALT, ALP, and T. Bilirubin. Direct Bilirubin (only if T. Bilirubin is elevated); GGT (if ALP increase is clinically significant)
Thyroid Test	X				X		X		X	TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration. **Every odd cycle D1**
Urinalysis	As clinically indicated. See Section 5.3.2.									
Pregnancy Test[f]	X				X	X	X		X	
Adverse Event Reporting										
[redacted]	[redacted]									

Table 5.1-5: On Treatment Procedural Outline Part 6 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with RCC)

(C1-C7, Additional Cycles) Cycle = 3 weeks for C1-C4 Cycle = 4 weeks for C5 and beyond	C1				C2-C3	C4	C5-Beyond			Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**D15**	**EOT[a,b,c]**	**Notes[d]**
Monitor for Non-Serious Adverse Events	Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.									
Monitor for Serious Adverse Events	See note in screening procedures (Table 5.1-1)									
Pharmacokinetic Assessments	See Table 5.5.1-6 for specific samples at each cycle during the study.									
Serial Serum PK Sampling BMS-986178	See Table 5.5.1-6 for specific samples at each cycle during the study.									
BMS-986178 ADA Sampling	See Table 5.5.1-6 for specific samples at each cycle during the study.									
Serial Serum PK Sampling for Nivolumab	See Table 5.5.1-6 for specific samples at each cycle during the study.									
Nivolumab ADA Sampling	See Table 5.5.1-6 for specific samples at each cycle during the study.									
Serial Serum PK Sampling for Ipilimumab	See Table 5.5.1-6 for specific samples at each cycle during the study.									

Table 5.1-5: On Treatment Procedural Outline Part 6 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with RCC)

(C1-C7, Additional Cycles) Cycle = 3 weeks for C1-C4 Cycle = 4 weeks for C5 and beyond	C1				C2-C3	C4	C5-Beyond			Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**D15**	**EOT[a,b,c]**	**Notes[d]**
Ipilimumab ADA sampling	See Table 5.5.1-6 for specific samples at each cycle during the study.									
Biomarker Assessments	See Table 5.6-2 for specific samples at each cycle during the study.									
Blood RNA, Blood RO	See Table 5.6-2 for specific samples at each cycle during the study.									
Blood PD	See Table 5.6-2 for specific samples at each cycle during the study.									
PBMC	See Table 5.6-2 for specific samples at each cycle during the study.									
Blood Multiparameter Flow	See Table 5.6-2 for specific samples at each cycle during the study.									
Serum Factors	See Table 5.6-2 for specific samples at each cycle during the study.									
PD Plasma	See Table 5.6-2 for specific samples at each cycle during the study.									
Mandatory Fresh Tumor Biopsy	See Table 5.6-2 for specific samples at each cycle during the study.									
Blood TCR	See Table 5.6-2 for specific samples at each cycle during the study.									

Table 5.1-5: On Treatment Procedural Outline Part 6 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with RCC)

(C1-C7, Additional Cycles) Cycle = 3 weeks for C1-C4 Cycle = 4 weeks for C5 and beyond	**C1**				**C2-C3**	**C4**	**C5-Beyond**			**Window (± 2 days)**
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**D15**	**EOT[a,b,c]**	**Notes[d]**
Efficacy Assessments										
Tumor Assessments	Every 8 weeks (± 1 week) Note: If subject completes 24 weeks of dosing, C7D21 will be the last cycle visit (EOT), this will be at Week 24, and the 27 week scan should be done at this time.									By methods used at baseline. Same modality should be used for all assessments. Assessed by RECIST v1.1; see Appendix 3. Assessment to be performed prior to initiating next cycle of treatment. An unconfirmed PR or unconfirmed CR must be confirmed at least 4 weeks after initial assessment.
Brain Imaging	As clinically indicated									
Bone Scan	As clinically indicated									
Clinical Drug Supplies										
BMS-986178 **(C1-C4, q3w; C5 and beyond, q4w)**	Dosing will be on C1D1, C2D1, C3D1, C4D1, C5D1, C6D1, and C7D1, which corresponds to Weeks 1, 4, 7, 10, 13, 17, and 21									Supplied by BMS Use vials assigned per IRT
Nivolumab (240 mg flat dose) **(C1-C4, q3w)**	Dosing will be on C1D1, C2D1, C3D1, and C4D1, which corresponds to Weeks 1, 4, 7, and 10									Supplied by BMS Use vials assigned per IRT

Table 5.1-5: On Treatment Procedural Outline Part 6 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with RCC)

(C1-C7, Additional Cycles) Cycle = 3 weeks for C1-C4 Cycle = 4 weeks for C5 and beyond	**C1**				**C2-C3**	**C4**	**C5-Beyond**			**Window (± 2 days)**
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**D15**	**EOT[a,b,c]**	**Notes[d]**
Nivolumab (480 mg flat dose) **(C5 and beyond, q4w)**	Dosing will be on C5D1, C6D1, and C7D1, which corresponds to Weeks 13, 17, and 21									Supplied by BMS Use vials assigned per IRT
Ipilimumab (1 mg/kg) **(C1-C4, q3w)**	Dosing will be on C1D1, C2D1, C3D1, and C4D1, which corresponds to Weeks 1, 4, 7, and 10									Supplied by BMS Use vials assigned per IRT

Abbreviations: ADA = anti-drug antibody; AFP = alpha fetal protein; BMS = Bristol-Myers Squibb; C = Cycle; CBC = complete blood count; CEA = carcinoembryonic antigen; CR = complete response; CRC = colorectal cancer; D = Day; ECG = electrocardiogram; EOT = end of treatment; LFT = liver function test; IRT = Interactive Response Technology; LFT = liver function test; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PR = partial response; PSA = Prostate-Specific Antigen; RNA = ribonucleic acid; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; VS = vital signs.

[a] EOT is defined as the visit where the decision is made to discontinue the subject from treatment.

[b] For subjects who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C7D21) and the start of the Week 1 Safety Follow-up visit.

[c] For subjects who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated and will be considered the start of the Week 1 Safety Follow-up visit.

[d] Subjects will have procedures listed in this table completed at all cycles. For C1 to C4, 1 cycle = 3 weeks, and for C5 and beyond, 1 cycle = 4 weeks. Subjects who have additional cycles will follow this same time and events table.

[e] For BMS-986178, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion, except for C1D1 and C2D1 (where vital signs will be obtained every 30 minutes until 4 hours post infusion). Vital signs will be obtained before the infusion and then every 30 minutes (± 10 minutes) until the start of the next study drug infusion or per institution guidelines for administration of ipilimumab and/or nivolumab. The 30-minute post nivolumab infusion VS may correspond to the pre-infusion ipilimumab or BMS-986178 VS and the 30-minute post ipilimumab infusion VS may correspond to the pre-infusion BMS-986178 VS. In the event the next study drug administration is delayed, nivolumab and/or ipilimumab vital signs will be obtained until 60 minutes after completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.

[f] Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If the pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue and immediately notify the BMS Medical Monitor/designee per Section 6.4.

Table 5.1-6: On Treatment Procedural Outline Part 7 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with NSCLC)

(C1-C4, Additional Cycles) (Cycle = 6 weeks)	C1						C2-C4			C5-Beyond				Window (± 2 Days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D22**	**D29**	**D1**	**D15**	**D29**	**D1**	**D15**	**D29**	**EOT a,b,c**	**Notes[d]**
Safety Assessments														
Physical Examination (PE)	X												X	Predose (C1 only); See note in screening.
Symptom-directed PE		X	X	X	X	X	X	X	X	X				To include signs and symptoms
Physical Measurements	X			X		X	X	X	X	X				Weight only
Vital Signs	X	X		X		X	X	X	X	X			X	See note in screening.[e] Observe subjects 4 hours post-infusion C1D1 and C2D1
12-Lead Electrocardiogram (ECG)	X						X							All ECG tests should be performed as a single measurement. ECGs will be done at both predose and 4 hours when BMS-986178 PK sample is collected (ECGs should be done prior to the PK sample) at C1D1 and C4D1.
Laboratory Tests	See note in screening procedures and Section 5.3.2. Predose on D1.													
Chemistry (Excluding LFTs)	X	X	X	X	X	X	X	X	X	X			X	
CBC with Differential and Platelets	X	X	X	X	X	X	X	X	X	X			X	

Table 5.1-6: On Treatment Procedural Outline Part 7 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with NSCLC)

(C1-C4, Additional Cycles) (Cycle = 6 weeks)	C1						C2-C4			C5-Beyond				Window (± 2 Days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D22**	**D29**	**D1**	**D15**	**D29**	**D1**	**D15**	**D29**	**EOT a,b,c**	**Notes[d]**
LFT Assessment	X	X	X	X	X	X	X	X	X	X			X	AST, ALT, ALP, and T. Bilirubin. Direct Bilirubin (only if T. Bilirubin is elevated); GGT (if ALP increase is clinically significant)
Thyroid Test	X						X			X			X	TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Urinalysis	As clinically indicated. See Section 5.3.2.													
Pregnancy Test[f]	X			X		X	X	X	X	X			X	
Adverse Event (AE) Reporting														
[redacted]	[redacted]													
Monitor for Non-Serious Adverse Events	Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.													
Monitor for Serious Adverse Events	See note in screening procedures (Table 5.1-1).													
Pharmacokinetic Assessments	See Table 5.5.1-5 for specific samples at each cycle during the study.													

Table 5.1-6: On Treatment Procedural Outline Part 7 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with NSCLC)

(C1-C4, Additional Cycles) (Cycle = 6 weeks)	C1						C2-C4			C5-Beyond				Window (± 2 Days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D22**	**D29**	**D1**	**D15**	**D29**	**D1**	**D15**	**D29**	**EOT a,b,c**	**Notes[d]**
Serial Serum PK Sampling for BMS-986178	See Table 5.5.1-5 for specific samples at each cycle during the study.													
BMS-986178 ADA Sample	See Table 5.5.1-5 for specific samples at each cycle during the study.													
Serial Serum PK Sampling for Nivolumab	See Table 5.5.1-5 for specific samples at each cycle during the study.													
Nivolumab ADA Sample	See Table 5.5.1-5 for specific samples at each cycle during the study.													
Serial Serum PK Sampling for Ipilimumab	See Table 5.5.1-5 for specific samples at each cycle during the study.													
Ipilimumab ADA Sample	See Table 5.5.1-5 for specific samples at each cycle during the study.													
Biomarker Assessments	See Table 5.6-4 for specific samples at each cycle during the study.													
Blood RNA, Blood RO	See Table 5.6-4 for specific samples at each cycle during the study.													
Blood PD	See Table 5.6-4 for specific samples at each cycle during the study.													
PBMC	See Table 5.6-4 for specific samples at each cycle during the study.													

Table 5.1-6: On Treatment Procedural Outline Part 7 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with NSCLC)

(C1-C4, Additional Cycles) (Cycle = 6 weeks)	C1						C2-C4			C5-Beyond				Window (± 2 Days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D22**	**D29**	**D1**	**D15**	**D29**	**D1**	**D15**	**D29**	**EOT a,b,c**	**Notes[d]**
Blood Multiparameter Flow	See Table 5.6-4 for specific samples at each cycle during the study.													
Serum Factors	See Table 5.6-4 for specific samples at each cycle during the study.													
PD Plasma	See Table 5.6-4 for specific samples at each cycle during the study.													
Mandatory Fresh Tumor Biopsy	See Table 5.6-4 for specific samples at each cycle during the study.													
Blood TCR	See Table 5.6-4 for specific samples at each cycle during the study.													
Efficacy Assessments														
Tumor Assessments	Every 8 weeks (± 1 week)												X	By methods used at baseline. Same modality/ should be used for all assessments. Assessed by RECIST v1.1; see Appendix 3. Assessment to be performed prior to initiating next cycle of treatment. An unconfirmed PR or unconfirmed CR must be confirmed at least 4 weeks after initial assessment.
Brain Imaging	As clinically indicated													
Bone Scan	As clinically indicated													

Table 5.1-6: On Treatment Procedural Outline Part 7 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with NSCLC)

(C1-C4, Additional Cycles) (Cycle = 6 weeks)	C1						C2-C4			C5-Beyond				Window (± 2 Days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D22**	**D29**	**D1**	**D15**	**D29**	**D1**	**D15**	**D29**	**EOT [a,b,c]**	**Notes[d]**
Clinical Drug Supplies														
BMS-986178 (q2w)	Dosing will be on C1D1, C1D15, C1D29, C2D1, C2D15, C2D29, C3D1, C3D15, C3D29, C4D1, C4D15, and C4D29, which corresponds to Weeks 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23									X	X	X		Supplied by BMS Use vials assigned per IRT
Nivolumab (240 mg q2w Flat Dose)	Dosing will be on C1D1, C1D15, C1D29, C2D1, C2D15, C2D29, C3D1, C3D15, C3D29, C4D1, C4D15, and C4D29, which corresponds to Weeks 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23									X	X	X		Supplied by BMS Use vials assigned per IRT
Ipilimumab (1 mg/kg q6w)	Dosing will be on Day 1 of each cycle,									X				Supplied by BMS Use vials assigned per IRT

Abbreviations: ADA = anti-drug antibody; AFP = alpha fetal protein; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BMS = Bristol-Myers Squibb; C = Cycle; CBC = complete blood count; CEA = carcinoembryonic antigen; CR = complete response; CRC = colorectal cancer; D = Day; EOT = end of treatment; LFT = liver function test; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IRT = Interactive Response Technology; LFT = liver function test; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PR = partial response; PSA = Prostate-Specific Antigen; RNA = ribonucleic acid; RO = receptor occupancy; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; VS = vital signs.

[a] EOT is defined as the visit where the decision is made to discontinue the subject from treatment.

[b] For subjects who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C4D35) and the start of the Week 1 Safety Follow-up visit.

[c] For subjects who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated and will be considered the start of the Week 1 Safety Follow-up visit.

[d] Subjects will have procedures listed in this table completed at all cycles. One cycle = 6 weeks. Subjects who have additional cycles will follow this same time and events table. BMS-986178, nivolumab, and ipilimumab will continue for all additional cycles.

[e] For BMS-986178, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion, except for C1D1 and C2D1 (where vital signs will be obtained every 30 minutes until 4 hours post infusion). Vital signs will be obtained before the infusion and then every 30 minutes (± 10 minutes) until the start of the next study drug infusion or per institution guidelines for administration of ipilimumab and nivolumab. The 30-minute post nivolumab infusion VS may correspond to the pre-infusion ipilimumab VS and the 30-minute post ipilimumab infusion VS may correspond to the pre-infusion BMS-986178 VS. In the event the next study drug administration is delayed, nivolumab and/or ipilimumab vital signs will be obtained until 60 minutes after completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.

[f] Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If the pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue and immediately notify the BMS Medical Monitor/designee per Section 6.4.

Table 5.1-7: On Treatment Procedural Outline Part 8 (CA012004 - q12w Dosing)

(C1-C8) (Cycle = 12 weeks)	C1-C2					C3-beyond					Window (± 2 Days)
Procedure	**D1**	**D8**	**D15**	**D29**	**D57**	**D1**	**D15**	**D29**	**D57**	**EOT [a,b,c]**	**Notes[d]**
Safety Assessments											
Physical Examination (PE)	X		X							X	Predose (C1 only); See note in screening.
Symptom-directed PE		X		X	X	X	X	X	X		To include signs and symptoms;
Physical Measurements	X		X	X	X	X	X	X	X		Weight only
Vital Signs	X		X	X	X	X	X	X	X	X	See note in screening.[e] Observe subjects 4 hours post-infusion C1D1 and C2D1
12-Lead Electrocardiogram (ECG)	X										All ECG tests should be performed as a single measurement. ECGs will be done at both predose and 4 hours when BMS-986178 PK sample is collected (ECGs should be done prior to the PK sample) at C1D1 and C2D1.
Laboratory Tests	See note in screening procedures and Section 5.3.2. Predose on all dosing days										
Chemistry (Excluding LFTs)	X	X	X	X	X	X	X	X	X	X	
CBC with Differential and Platelets	X	X	X	X	X	X	X	X	X	X	

Table 5.1-7: On Treatment Procedural Outline Part 8 (CA012004 - q12w Dosing)

(C1-C8) (Cycle = 12 weeks)	C1-C2					C3-beyond					Window (± 2 Days)
Procedure	**D1**	**D8**	**D15**	**D29**	**D57**	**D1**	**D15**	**D29**	**D57**	**EOT [a,b,c]**	**Notes[d]**
LFT Assessment	X	X	X	X	X	X	X	X	X	X	AST, ALT, ALP, and T. Bilirubin. Direct Bilirubin (only if T. Bilirubin is elevated); GGT (if ALP increase is clinically significant)
Thyroid Test	X					X				X	TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Tumor Markers	X			X	X	X		X	X	X	
Urinalysis	As clinically indicated. See Section 5.3.2.										
Pregnancy Test[f]	X			X	X	X		X	X	X	
Adverse Event (AE) Reporting											
[redacted]			[redacted]								
Monitor for Non-Serious Adverse Events			Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.								
Monitor for Serious Adverse Events			See note in screening procedures (Table 5.1-1).								

Table 5.1-7: On Treatment Procedural Outline Part 8 (CA012004 - q12w Dosing)

(C1-C8) (Cycle = 12 weeks)	C1-C2					C3-beyond					Window (± 2 Days)
Procedure	**D1**	**D8**	**D15**	**D29**	**D57**	**D1**	**D15**	**D29**	**D57**	**EOT [a,b,c]**	**Notes[d]**
Pharmacokinetic Assessments			See Table 5.5.1-6 for specific samples at each cycle during the study.								
Serial Serum PK Sampling for BMS-986178 (cohort 1-3 only)			See Table 5.5.1-6 for specific samples at each cycle during the study.								
BMS-986178 ADA Sample (cohort 1-3 only)			See Table 5.5.1-6 for specific samples at each cycle during the study.								
Serial Serum PK Sampling for Nivolumab			See Table 5.5.1-6 for specific samples at each cycle during the study.								
Nivolumab ADA Sample			See Table 5.5.1-6 for specific samples at each cycle during the study.								
Biomarker Assessments			See Table 5.6-5 for specific samples at each cycle during the study.								
Blood RNA, Blood RO			See Table 5.6-5 for specific samples at each cycle during the study.								
Blood PD			See Table 5.6-5 for specific samples at each cycle during the study.								
PBMC			See Table 5.6-5 for specific samples at each cycle during the study.								
Blood Multiparameter Flow	See Table 5.6-5 for specific samples at each cycle during the study.										
Serum Factors	See Table 5.6-5 for specific samples at each cycle during the study.										

Table 5.1-7: On Treatment Procedural Outline Part 8 (CA012004 - q12w Dosing)

(C1-C8) (Cycle = 12 weeks)	**C1-C2**					**C3-beyond**					**Window (± 2 Days)**
Procedure	**D1**	**D8**	**D15**	**D29**	**D57**	**D1**	**D15**	**D29**	**D57**	**EOT [a,b,c]**	**Notes[d]**
PD Plasma	See Table 5.6-5 for specific samples at each cycle during the study.										
ctDNA	See Table 5.6-5 for specific samples at each cycle during the study.										
Mandatory Fresh Tumor Biopsy	See Table 5.6-5 for specific samples at each cycle during the study.										On treatment C1D15 and C1D78
Blood TCR	See Table 5.6-5 for specific samples at each cycle during the study.										
Efficacy Assessments											
Tumor Assessments	Every 12 weeks (± 1 week)									X	By methods used at baseline. Same modality/ should be used for all assessments. Assessed by RECIST v1.1; see Appendix 3. Assessment to be performed prior to initiating next cycle of treatment. An unconfirmed PR or unconfirmed CR must be confirmed at least 6 weeks after initial assessment.
Brain Imaging	As clinically indicated										
Bone Scan	As clinically indicated										

Table 5.1-7: On Treatment Procedural Outline Part 8 (CA012004 - q12w Dosing)

(C1-C8) (Cycle = 12 weeks)	C1-C2					C3-beyond					Window (± 2 Days)
Procedure	**D1**	**D8**	**D15**	**D29**	**D57**	**D1**	**D15**	**D29**	**D57**	**EOT [a,b,c]**	**Notes[d]**
Clinical Drug Supplies											
BMS-986178 (q12w) Cohort 1-3 Only	Dosing on Day 1 of each cycle										Supplied by BMS Use vials assigned per IRT
Nivolumab (480 mg Flat Dose q4w)	Dosing on Day 1, 29, and 57 of each cycle										Supplied by BMS Use vials assigned per IRT
Tetanus Vaccine	C1D1 Only										Locally Sourced

Abbreviations: ADA = anti-drug antibody; AFP = alpha fetal protein; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BMS = Bristol-Myers Squibb; C = Cycle; CBC = complete blood count; CEA = carcinoembryonic antigen; CR = complete response; CRC = colorectal cancer; D = Day; EOT = end of treatment; LFT = liver function test; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IRT = Interactive Response Technology; LFT = liver function test; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PR = partial response; PSA = Prostate-Specific Antigen; RNA = ribonucleic acid; RO = receptor occupancy; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; VS = vital signs.

[a] EOT is defined as the visit where the decision is made to discontinue the subject from treatment.

[b] For subjects who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C9D78) and the start of the Week 1 Safety Follow-up visit.

[c] For subjects who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated and will be considered the start of the Week 1 Safety Follow-up visit.

[d] Subjects will have procedures listed in this table completed at all cycles. One cycle = 12 weeks.

[e] For BMS-986178, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion, except for C1D1 and C2D1 (where vital signs will be obtained every 30 minutes until 4 hours post infusion). Vital signs will be obtained before the infusion and

then every 30 minutes (± 10 minutes) until the start of the next study drug infusion or per institution guidelines for administration of nivolumab. The 30-minute post nivolumab infusion VS may correspond to the pre-infusion BMS-986178 VS. In the event the next study drug administration is delayed, nivolumab vital signs will be obtained until 60 minutes after completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.

f Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If the pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue and immediately notify the BMS Medical Monitor/designee per Section 6.4.

Table 5.1-8: Follow-up Procedural Outline Parts 1 - 8 (CA012004)

Procedure	Safety Follow-up					
	FU 1 30 Days[a] (± 7 days)	**FU 2 60 Days (± 7 days)**	**FU 3 100 Days (± 10 days)**			**Notes**
Safety Assessments						
Physical Examination (PE)	X	X	X			
Vital Signs	X	X	X			Includes body temperature, seated blood pressure, and heart rate.
Laboratory Tests						
Chemistry (excluding LFTs)	X	X	X			See Section 5.3.2.
CBC with Differential and Platelets	X	X	X			
LFT Assessment	X	X	X			LFTs will be monitored following the last dose of BMS-986178. Includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated) alkaline phosphatase, and GGT (if ALP increase is clinically significant).
Urinalysis	As clinically indicated. See Section 5.3.2.					
Pregnancy Test	X	X	X			For WOCBP; serum or urine pregnancy test may be performed (clinic urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG). If positive, perform confirmatory testing. If pregnancy is confirmed, immediately notify the BMS Medical Monitor/designee per Section 6.4.

Table 5.1-8: Follow-up Procedural Outline Parts 1 - 8 (CA012004)

Procedure	Safety Follow-up					
	FU 1 30 Days[a] (± 7 days)	FU 2 60 Days (± 7 days)	FU 3 100 Days (± 10 days)			Notes
Adverse Event Reporting [redacted]						
Monitor for Non-Serious Adverse Events	X	X	X			Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.
Monitor for Serious Adverse Events	X	X	X			See note in screening procedures (Table 5.1-1).
[redacted]	[redacted]	[redacted]	[redacted]			
Sample Collection						
Pharmacokinetic Assessments	X	X	X	See Table 5.5.1-1 (Parts 1 and 2), Table 5.5.1-2 (Part 4), Table 5.5.1-3 (Parts 3 and 5), Table 5.5.1-6 (Part 6), Table 5.5.1-5 (Part 7), and Table 5.5.1-6 (Part 8).		
Immunogenicity (ADA) Assessments	X	X	X	See Table 5.5.1-1 (Parts 1 and 2), Table 5.5.1-2 (Part 4), Table 5.5.1-3 (Parts 3 and 5), Table 5.5.1-6 (Part 6) Part 6), Table 5.5.1-5 (Part 7) and Table 5.5.1-6 (Part 8).		

Table 5.1-8: Follow-up Procedural Outline Parts 1 - 8 (CA012004)

Procedure	Safety Follow-up					Notes
	FU 1 30 Days[a] (± 7 days)	**FU 2 60 Days (± 7 days)**	**FU 3 100 Days (± 10 days)**			
Efficacy Assessments						
Tumor / Response Assessments			X			Diagnostic imaging by method used at baseline; an unconfirmed PR or unconfirmed CR must be confirmed at least 4 weeks after initial assessment. Assessed by RECIST v1.1; see Appendix 3. Subjects who discontinue study drug must continue to be followed per the Safety Follow-up (approximately 100 days).
Subsequent Treatments (Anti-cancer)	X	X	X			

Abbreviations: ADA = anti-drug antibody; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BMS = Bristol-Myers Squibb; CBC = complete blood count; CR = complete response; EOT = end of treatment; FU = Follow-Up; LFT = liver function test; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; LFT = liver function test; PD = pharmacodynamic; PR = partial response; RO = receptor occupancy; SAE = serious adverse event; SD =stable disease; SOC = standard of care; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; WOCBP = women of child bearing potential.

[a] Follow-up visits at Days 30, 60 (±7 days), and 100 (±10 days) should occur after the last dose or coinciding with the date of discontinuation ±7 days if the date of discontinuation is greater than 30 days after the last dose to monitor for adverse events.

In the event that multiple procedures are required at a single time point, the following is a list of procedures from highest to lowest priority:

1) PK Sampling
2) Safety (ECG)
3) Safety (clinical laboratories)

5.1.1 Retesting During Screening

Retesting of laboratory parameters and/or other assessments within any single screening will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 5.1-1 may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor (or designee) may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

The site will provide all required materials for the tests performed locally (ie, relevant clinical laboratory tests and urine drug screens). The site will have a well-calibrated scale available for recording body weight, a 12-lead ECG machine, and a calibrated sphygmomanometer, a syringe pump, 0.2-µm filter infusion sets, and a thermometer for vital signs assessments. A current and fully stocked advanced cardiac life support cart will be immediately available on the premises. The site will have a refrigerated centrifuge, a monitored and alarmed refrigerator, and freezer (-70°C preferred, -20°C acceptable), as well as containers and dry ice for shipment and storage of blood samples. The site will provide all materials required for accurate source documentation of study activities and for housing the subjects during the study. The site will source marketed product from a single commercial lot.

BMS will provide a Sponsor-approved protocol and any amendments or administrative letters (if required) and an IB. CRFs (electronic or hard copy) will be provided by BMS. BMS/central laboratory will provide labels and tubes for the collection of blood samples for PK/PD and for genotyping analysis.

5.3 Safety Assessments

AEs will be assessed during the study and for 100 days after the last treatment. AEs will be evaluated according to NCI CTCAE v4.03 and should be followed per requirements in Section 6.1 and Section 6.2. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities and reviewed for potential significance and importance. Subjects should be followed until all treatment-related AEs have recovered to baseline or are deemed irreversible by the investigator.

Protocol-specified assessments are described in Table 5.1-1 (Screening), Table 5.1-2 (On Treatment - Parts 1 and 2), Table 5.1-3 (On Treatment - Parts 3 and 5), Table 5.1-4 (On Treatment - Part 4), Table 5.1-5 (On Treatment - Part 6), Table 5.1-6 (On Treatment - Part 7), Table 5.1-7 (On Treatment - Part 8), and Table 5.1-8 (Follow-up - Parts 1 - 8).

5.3.1 Imaging Assessment for the Study

1) CT/MRI

   a) Contrast-enhanced CT scans acquired on dedicated CT equipment is preferred for this study. CT with contrast of the chest, abdomen, and pelvis are to be performed for tumor assessments. CT scans should be acquired with 5-mm slices and no intervening gap (contiguous).

      (1). Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen and pelvis may be obtained. MRIs should be acquired with slice thickness of < 5 mm with no gap (contiguous).

      (2). Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.

      (3). Note on the use of the CT component of a positron emission tomography (PET)/CT scanner:

      Combined modality scanning such as with fluorodeoxyglucose (FDG)-PET/CT is increasingly used in clinical care and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low-dose or attenuation-correction CT portions of a combined FDG-PET/CT are of limited use in anatomically based efficacy assessments; it is therefore suggested that they should not be substituted for dedicated diagnostic contrast-enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the FDG-PET/CT can be used for RECIST 1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

2) Brain MRI

   a) MRI of the brain is required at screening if subject is symptomatic or has a history of brain metastasis. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks or sooner, if clinically indicated.

   b) MRI brain scans during on-study treatment and follow-up periods are required **only** if there is a prior history of lesions present at Screening, or as clinically indicated for new signs and symptoms that suggest central nervous system (CNS) involvement.

3) Bone Scan

   a) Bone scans can be used to evaluate metastatic disease.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

5.3.2 Laboratory Test Assessments

Each site's local laboratory will perform the analyses and will provide reference ranges for these tests.

Results of clinical laboratory tests performed on Day 1 must be available prior to dosing.

The following clinical laboratory tests will be performed:

Hematology

Hemoglobin
Hematocrit
Platelet count
Total leukocyte count, including differential

CBC and differential results will be monitored on an ongoing basis and should be sent to the local laboratory data service upon receipt of the results. Others will be sent to the local laboratory data service.

Serum Chemistry

AST
ALT
Amylase
Total bilirubin
Direct bilirubin (only as reflex when T bilirubin elevated)
ALP
Lactate dehydrogenase
Lipase
Creatinine
Blood urea nitrogen
Uric acid (at screening only)
Glucose (fasting at screening)
Gamma-glutamyl transferase (only as reflex when ALP increase is clinically significant)
Total protein
Albumin
Sodium
Potassium
Chloride
Calcium
C-reactive protein
Ferritin
Carbon dioxide
Phosphorus
Magnesium
CrCL(screening only)

Thyroid Laboratories

Thyroid-stimulating hormone (TSH)
Free T3 and free T4 (at screening and reflex when TSH abnormal)

Urinalysis

Protein
Glucose

Blood
Leukocyte esterase
Specific gravity
pH
Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive

Serology

Hepatitis B surface antigen
Serum for hepatitis C antibody(if Hep C Ab is positive reflex to Hep C RNA) or Hep C RNA, HIV-1 and -2 antibody (testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements).

Other Analyses

Pregnancy test (WOCBP only: serum testing at screening and within 24 hours prior to dosing; urine or serum at all other time points).
FSH (screening only for women only)

Tumor Specific Serum Markers

CA125 testing for all subjects with OC

Alpha fetal protein (AFP) testing for all subjects with hepatocellular carcinoma

Carcinoembryonic antigen (CEA) testing for all subjects with CRC

CA19-9 testing for all subjects with pancreatic cancer

Prostate-Specific Antigen test for all subjects with prostate cancer

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 6.3).

5.4 Efficacy Assessments

Disease assessment with CT and/or MRI as appropriate will be performed at baseline and every 8 weeks Parts 1-7 or every 12 weeks for Part 8 (± 1 week) per RECIST v1.1 (see Appendix 3) until discontinuation of treatment or withdrawal from study. Tumor assessments at other time points may be performed if the investigator is concerned about tumor progression. Assessment of tumor response will be reported by the investigator for appropriate populations of subjects as defined by RECIST v1.1[157] (see Appendix 3) for subjects with advanced solid tumors. The same modality should be used and the same scanner is preferred for all assessments.

Investigators will also report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the CRF based on the investigators'

assessment using RECIST criteria. Please refer to Appendix 3 for specifics of RECIST v1.1 criteria to be utilized in this study.

5.4.1 Primary Efficacy Assessment

Not applicable.

5.4.2 Secondary Efficacy Assessments

The efficacy assessments will include ORR (eg, PR and CR), duration of response, and progression-free survival rate (PFSR) at time points (eg, 24 weeks) based on assessment of tumor response using RECIST v1.1.

[redacted]

5.5 Pharmacokinetic Assessments

Samples for PK and immunogenicity assessments will be collected for subjects receiving BMS-986178 alone or in combination with nivolumab and/or ipilimumab, as described in Table 5.5.1-1 (Parts 1 and 2), Table 5.5.1-2 (Part 4), Table 5.5.1-3 (Parts 3 and 5), Table 5.5.1-6 (Part 6), Table 5.5.1-5 (Part 7), , and Table 5.5.1-6. The PK of BMS-986178 will be characterized by NCA method. Immunogenicity samples will be analyzed for anti-BMS-986178 antibodies and/or anti-nivolumab antibodies and/or anti-ipilimumab antibodies by validated immunoassays.

If data permit, the PK parameters might be assessed following Cycle 1 Day 1 and Cycle 9 Day 1 for the q2w dosing regimen in monotherapy or in combination therapy, Cycle 4 Day 1 for the q3w or q6w dosing regimen in combination therapy with ipilimumab and/or nivolumab combination therapy, Cycle 5 Day 1 for q4w dosing regimen in combination therapy with nivolumab include the following:

Cmax	Maximum observed serum concentration
Tmax	Time of maximum observed concentration
AUC(0-t)	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(TAU)	Area under the concentration-time curve in 1 dosing interval

In addition, the PK parameters listed below may be assessed following dose administration in Cycle 9 Day 1 for the q2w or Cycle 5 Day 1 for q4w dosing regimen in monotherapy or in combination therapy and Cycle 4 Day 1 for the q3w and q6w dosing regimen in combination therapy with ipilimumab and/or nivolumab.

Ctau	The observed concentration at the end of a dosing interval
CLT	Total body clearance
Css-avg	Average concentration over a dosing interval (AUC(TAU)/tau)
AI	Ratio of an exposure measure at steady state (eg, following Cycle 9 Day 1 dose) to that after the first dose (exposure measure includes AUC(TAU), Cmax and Ctau).

T-HALFeff	Effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure (exposure measure includes AUC(TAU), Cmax and Ctau)

The following PK parameter will be reported as a separate listing, summary, and plot:

Ctrough	Trough observed plasma concentrations (this includes predose concentrations (C0) and Ctau)

5.5.1 Pharmacokinetics and Immunogenicity Collection and Processing

Detailed sampling schedules to be followed for the assessment of PK and immunogenicity for BMS-986178 monotherapy or in combination therapy are provided in Table 5.5.1-1 (Parts 1 and 2), Table 5.5.1-2 (Part 4), Table 5.5.1-3 (Parts 3 and 5), Table 5.5.1-6 (Part 6), Table 5.5.1-5 (Part 7), and Table 5.5.1-6 (Part 8). However, if there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit).

All predose samples should be taken within 30 minutes before the start of any dose infusion. All postdose PK sampling time points are relative to the start of BMS-986178 administration. End-of-infusion samples should be taken just prior to the end of infusion (EOI; preferably within 2 minutes). Further details of sample collection, processing, and shipment will be provided in the laboratory procedure manual. On-treatment PK samples are intended to be drawn relative to actual dosing days; if a dose occurs on a different day within the cycle due to delays or minor schedule adjustments, PK samples should be adjusted accordingly.

Table 5.5.1-1: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 Monotherapy or in Combination Therapy - Parts 1 and 2 (CA012004 - q2w Dosing)

Study Day of Sample Collection (1 Cycle = 2 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	BMS-986178 PK Sample (All Subjects)	Nivolumab PK Sample (Part 2)	BMS-986178 ADA Sample (All Subjects)	Nivolumab ADA Sample (Part 2)
C1D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
		04:00	X			
C1D2		24:00	X			
C1D4[c]		72:00	X			
C1D8[d]		168:00	X			
C2D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
C3D1	Predose[a]	00:00[a]	X	X	X	X
C4D1	Predose[a]	00:00[a]	X	X		
End of Treatment						
Unscheduled[e]			X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = Cycle; D = Day; EOI = end of infusion.

[a] Predose: All predose samples for combinations should be collected prior to the start of the first infusion.

[b] EOI samples for both nivolumab and BMS-986178 should be collected at the end of the BMS-986178 infusion. The EOI sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] D4 sample may be taken during D3 to D5 of a cycle.

[d] D8 sample may be taken during D7 to D9 of a cycle.

[e] Unscheduled: If there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit).

Table 5.5.1-2: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 in Combination Therapy - Part 4 (CA012004 - q4w Dosing)

Study Day of Sample Collection (1 Cycle = 4 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	BMS-986178 PK Sample	Nivolumab PK Sample	BMS-986178 ADA Sample	Nivolumab ADA Sample
C1D1s	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
		04:00	X			
C1D2		24:00	X			
C1D4[c]		72:00	X			
C1D8[d]		168:00	X			
C1D15[e]		336:00	X			
C2D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
C3D1	Predose[a]	00:00[a]	X	X	X	X
C4D1	Predose[a]	00:00[a]	X	X	X	X
End of Treatment						
Unscheduled[f]			X	X	X	X

[a] Predose: All predose samples for combinations should be collected prior to the start of the first infusion.

Abbreviations: ADA = anti-drug antibody; C = Cycle; D = Day; EOI = end of infusion.

[b] EOI samples for both nivolumab and BMS-986178 should be collected at the end of the BMS-986178 infusion. The EOI sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] D4 sample may be taken during D3 to D5 of a cycle.

[d] D8 sample may be taken during D7 to D9 of a cycle.

[e] D15 sample may be taken during D12 to D18 of a cycle.

[f] Unscheduled: If there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit).

Note: The time recorded is relative to BMS-986178 infusion.

Table 5.5.1-3: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 in Combination with Ipilimumab - Parts 3 and 5 (CA012004 - q3w Dosing)

Study Day of Sample Collection (1 Cycle = 3 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	BMS-986178 PK Sample	Ipilimumab PK Sample	BMS-986178 ADA Sample	Ipilimumab ADA Sample
C1D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
		04:00	X			
C1D2		24:00	X			
C1D4[c]		72:00	X			
C1D8[d]		168:00	X			
C1D15[d]		336:00	X			
C2D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
C3D1	Predose[a]	00:00[a]	X	X	X	X
C4D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
		04:00	X			
C4D2		24:00	X			
C4D4[c]		72:00	X			
C4D8[d]		168:00	X			
C4D15[d]		336:00	X			
End of Treatment						
Unscheduled[e]			X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = Cycle; D = Day; EOI = end of infusion; FU = Follow-Up.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Predose: All predose samples for combinations should be collected prior to the start of the first infusion.

[b] EOI samples for both ipilimumab and BMS-986178 should be collected at the end of the BMS-986178 infusion. The EOI sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to

the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] D4 sample may be taken during D3 to D5 of a cycle.

[d] D8 sample may be taken during D7 to D9 of a cycle; Day 15 sample may be taken during D13 to D17 of a cycle.

e Unscheduled: If there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit).

Table 5.5.1-4: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 in Combination - Part 6 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with RCC)

Study Day of Sample Collection (Cycle = 3 Weeks for C1 - C4 Cycle = 4 Weeks for C5 and Beyond)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	BMS-986178 PK Sample	Nivolumab PK Sample	Ipilimumab PK Sample	BMS-986178 ADA Sample	Nivolumab ADA Sample	Ipilimumab ADA Sample
C1D1	Predose[a]	00:00[a]	X	X	X	X	X	X
	EOI[b]	00:30[b]	X	X	X			
		04:00	X					
C1D2		24:00	X					
C1D4[c]		72:00	X					
C1D8[d]		168:00	X					
C1D15[e]		336:00	X					
C2D1	Predose[a]	00:00[a]	X	X	X	X	X	X
	EOI[b]	00:30[b]	X	X	X			
C3D1	Predose[a]	00:00[a]	X	X	X	X	X	X
C4D1	Predose[a]	00:00[a]	X	X	X	X	X	X
	EOI[b]	00:30[b]	X	X	X			
		04:00	X					
C4D2		24:00	X					
C4D4[c]		72:00	X					

Table 5.5.1-4: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 in Combination - Part 6 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with RCC)

Study Day of Sample Collection (Cycle = 3 Weeks for C1 - C4 Cycle = 4 Weeks for C5 and Beyond)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	BMS-986178 PK Sample	Nivolumab PK Sample	Ipilimumab PK Sample	BMS-986178 ADA Sample	Nivolumab ADA Sample	Ipilimumab ADA Sample
C4D8[d]		168:00	X					
C4D15[e]		336:00	X					
		End of Treatment						
Unscheduled[f]			X	X	X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = Cycle; D = Day; EOI = end of infusion.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Predose: All predose samples for combinations should be collected prior to the start of the first infusion.

[b] EOI samples for ipilimumab, nivolumab, and BMS-986178 should be collected at the end of the BMS-986178 infusion. The EOI sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] D4 sample may be taken during D3 to D5 of a cycle.

[d] D8 sample may be taken during D7 to D9 of a cycle.

[e] D15 sample may be taken during D13 to D17 of a cycle.

[f] Unscheduled: If there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit).

Table 5.5.1-5: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 in Combination - Part 7 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with NSCLC)

Study Day of Sample Collection (1 Cycle = 6 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	BMS-986178 PK Sample	Nivolumab PK Sample	Ipilimumab PK Sample	BMS-986178 ADA Sample	Nivolumab ADA Sample	Ipilimumab ADA Sample
C1D1	Predose[a]	00:00[a]	X	X	X	X	X	X
	EOI[b]	00:30[b]	X	X	X			
		04:00	X					
C1D2		24:00	X					
C1D4[c]		72:00	X					
C1D8[d]		168:00	X					
C1D15[e]	Predose[a]	00:00[a]	X	X				
C1D29[f]	Predose[a]	00:00[a]	X	X				
C2D1	Predose[a]	00:00[a]	X	X	X	X	X	X
	EOI[b]	00:30[b]	X	X	X			
C3D1	Predose[a]	00:00[a]	X	X	X	X	X	X
C4D1	Predose[a]	00:00[a]	X	X	X	X	X	X
	EOI[b]	00:30[b]	X	X	X			
		04:00	X					
C4D2		24:00	X					
C4D4[c]		72:00	X					

Table 5.5.1-5: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 in Combination - Part 7 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with NSCLC)

Study Day of Sample Collection (1 Cycle = 6 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	BMS-986178 PK Sample	Nivolumab PK Sample	Ipilimumab PK Sample	BMS-986178 ADA Sample	Nivolumab ADA Sample	Ipilimumab ADA Sample
C4D8[d]		168:00	X					
C4D15[e]	Predose[a]	00:00[a]	X	X				
C4D29[f]	Predose[a]	00:00[a]	X	X				
		End of Treatment						
Unscheduled[g]			X	X	X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = Cycle; D = Day; EOI = end of infusion.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Predose: All predose samples for combinations should be collected prior to the start of the first infusion.

[b] EOI samples for ipilimumab, nivolumab, and BMS-986178 should be collected at the end of the BMS-986178 infusion. The EOI sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly

[c] D4 sample may be taken during D3 to D5 of a cycle.

[d] D8 sample may be taken during D7 to D9 of a cycle.

[e] D15 sample may be taken during D13 to D17 of a cycle.

[f] D29 sample may be taken during D26 to D30 of a cycle.

[g] Unscheduled: If there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit).

Table 5.5.1-6: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 in Combination - Part 8 (CA012004 - q12w Dosing)

Study Day of Sample Collection (1 Cycle = 12 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	BMS-986178 PK Sample (Cohort 1-3)	Nivolumab PK Sample	BMS-986178 ADA Sample (Cohort 1-3)	Nivolumab ADA Sample
C1D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
		04:00	X			
C1D8[c]		168:00	X	X		
C1D15[d]		336:00	X	X		
C1D29[e]		696:00	X	X	X	X
C2D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
		04:00	X			
C2D8[c]		168:00	X	X		
C2D15[d]		336:00	X			
C2D29[e]		696:00	X	X		
C3D1	Predose[a]	00:00[a]	X	X	X	X
End of Treatment						
Unscheduled[f]			X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = Cycle; D = Day; EOI = end of infusion.
Note: The time recorded is relative to BMS-986178 infusion.

[a] Predose: All predose samples for combinations should be collected prior to the start of the first infusion.

[b] EOI samples for both nivolumab and BMS-986178 should be collected at the end of the BMS-986178 infusion. The EOI sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] D8 sample may be taken during D7 to D9 of a cycle.

[d] D15 sample may be taken during D12 to D18 of a cycle.

[e] D29 sample may be taken prior nivolumab infusion.

[f] Unscheduled: If there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit).

5.5.2 Pharmacokinetic and Immunogenicity Sample Analyses

The serum samples will be analyzed for drug (BMS-986178 and/or nivolumab and/or ipilimumab) and ADA (anti-BMS-986178 antibodies and/or anti-nivolumab antibodies and/or anti-ipilimumab antibodies) by validated immunoassays. In addition, selected serum samples may be analyzed by an exploratory method that measures BMS-986178, nivolumab, and ipilimumab; or detect ADAs for technology exploration purposes; exploratory results will not be reported. Serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity-related AE).

5.5.3 Labeling and Shipping of Biological Samples

Detailed instructions for the PK blood collection, labeling, processing, storage, and shipping will be provided to the site in the laboratory procedure manual.

5.6 Biomarker Assessments

To assess the PD effects of BMS-986178 as well as receptor occupancy (RO) in relation to dose and PK, whole blood samples (blood PD and blood RO) will be collected at the times indicated in Table 5.6-1 (Parts 1 and 2), Table 5.6-2 (Parts 3, 5, and 6), Table 5.6-3 (Part 4), Table 5.6-4 (Part 7), and Table 5.6-5 (Part 8). The sample testing plans associated with each are described in Section 5.7. Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided in a separate laboratory procedure manual.

Blood samples for PD assessment will be analyzed by cytometry to determine baseline and serial on-treatment alterations in composition and/or activation status of lymphocyte subsets. Lymphocyte subsets to be assayed may include, but are not limited to, CD8+ and CD4+ T-cell subsets (activated; effector/memory; regulatory) and populations of those cells as defined by the expression of proliferation, activation, exhaustion, or signaling markers such as KI67, HLA-DR, PD-1, etc. Treatment-induced alterations in blood lymphocyte populations will be analyzed in relation to both dose and blood concentrations of BMS-986178.

Receptor occupancy of OX40 by BMS-986178 (RO) on peripheral blood mononuclear cells (PBMCs) may also be determined by flow cytometry. RO will be analyzed in relation to PK and PD effects. Samples will be collected to determine RO from subjects in Part 1A and 1B in this study. For combination cohorts, a blood tube will also be collected for exploratory purposes to measure pharmacodynamic endpoints including, but not limited to RO.

Table 5.6-1: Pharmacodynamic and Exploratory Biomarker Sampling Schedule for BMS-986178 Monotherapy and Combination Therapy - Parts 1 and 2 (CA012004 - q2w Dosing)

Study Day of Sample Collection (1 Cycle = 2 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	Blood RNA, Blood RO[a]	Blood PD	PBMC, Blood Multiparameter Flow, Serum Factors, Plasma[b]	Tumor Biopsy[c] Section 5.6	Blood Genotype, Blood TCR[d]	Archived Tumor[e]
Screening				X		X	X	X
C1D1	Predose[f]	00:00	X	X	X			
C1D2		24:00			X			
C1D8[g]		168:00	X	X	X			
C2D1	Predose[f]	00:00	X	X	X	X[h]		
C3D1	Predose[f]	00:00		X	X		X	
EOT/Unscheduled/ Progression	EOT			X	X	X	X	

Abbreviations: C = Cycle; D = Day; EOT = end of treatment; FFPE = formalin-fixed, paraffin-embedded; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; RNA = ribonucleic acid; RO = receptor occupancy; TCR = T cell receptor.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Separate samples will be collected for blood RNA and blood RO assessments. Blood RNA samples will be collected from all subjects. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[b] Separate samples will be collected for PBMC, blood multiparameter flow, serum factors, and plasma assessments. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[c] Mandatory predose and on-treatment biopsies for all subjects. Additional subjects may be added in the event that some subjects do not have obtainable tumor at the on-treatment time point. Subjects obtaining biopsies should have adequate tissue collected as outlined in the laboratory manual. Additional optional biopsies may be collected at EOT, time of disease progression, or during another clinically meaningful event (eg, response or adverse event).

[d] Blood genotype sample to be collected at screening only

[e] All subjects may provide an archived tumor specimen. Archival FFPE block or a minimum of 15 slides is required; 25 slides are preferred. See laboratory manual.

[f] Predose: All predose samples for combinations should be taken prior to the start of the first infusion.

[g] D8 sample may be taken during D7 to D9 of a cycle.

[h] C2D1 fresh tumor biopsy may be taken during C1D12-C2D4.

Table 5.6-2: Pharmacodynamic and Exploratory Biomarker Sampling Schedule for BMS-986178 Combination Therapy - Parts 3, 5, and 6 (CA012004)

Study Day of Sample Collection (Cycle = 3 Weeks for C1 - C8 for Parts 3 and 5) (Cycle = 3 Weeks for C1 - C4 Cycle = 4 Weeks for C5 and Beyond for Part 6)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	Blood RO, Blood RNA[a]	Blood PD	PBMC, Blood Multiparameter Flow, Serum Factors, Plasma[b]	Tumor Biopsy[c]	Blood Genotype, Blood TCR[d]	Archived Tumor[e]
Screening				X		X	X	X
C1D1	Predose[f]	00:00	X	X	X			
C1D2		24:00			X			
C1D8[g]		168:00	X	X	X			
C1D15[h]		336:00	X	X	X	X		
C2D1	Predose[f]	00:00	X	X	X		X	
C2D8								
C3D1	Predose[f]	00:00	X	X	X			
C4D1	Predose[f]	00:00	X	X	X		X	
EOT/Unscheduled/ Progression	EOT			X	X	X	X	

Abbreviations: C = Cycle; D = Day; EOT = end of treatment; FFPE = formalin-fixed, paraffin-embedded; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; RO=Receptor Occupancy RNA = ribonucleic acid; TCR = T cell receptor.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Separate samples will be collected for blood RNA and blood RO assessments from all subjects. Detailed instructions for the collection, processing, and shipping of samples will be provided in the laboratory procedure manual.

[b] Separate samples will be collected for PBMC, blood multiparameter flow, serum factors, and plasma assessments. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[c] Mandatory predose and on-treatment biopsies for all subjects. Additional subjects may be added in the event that some subjects do not have obtainable tumor at the on-treatment time point. Subjects obtaining biopsies should have adequate tissue collected as outlined in the laboratory manual. Additional optional biopsies may be collected at EOT, time of disease progression, or during another clinically meaningful event (eg, response or adverse event).

[d] Blood genotype sample to be collected at screening only.

[e] All subjects may provide an archived tumor specimen. Archival FFPE block or a minimum of 15 slides is required; 25 slides are preferred. See laboratory manual.

[f] Predose: All predose samples for combinations should be taken prior to the start of the first infusion.

[g] D8 sample may be taken during D7 to D9 of a cycle.

[h] D15 sample may be taken during D13 to D17 of a cycle.

Table 5.6-3: Pharmacodynamic and Exploratory Biomarker Sampling Schedule for BMS-986178 Combination Therapy - Part 4 (CA012004 - q4w Dosing)

Study Day of Sample Collection (1 Cycle = 4 Weeks	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	Blood RNA, Blood RO[a]	Blood PD	PBMC, Blood Multiparameter Flow, Serum Factors, Plasma[b]	Tumor Biopsy[c]	Blood Genotype, Blood TCR[d]	Archived Tumor[e]
Screening				X		X	X	X
C1D1	Predose[f]	00:00	X	X	X			
C1D2		24:00			X			
C1D8[g]		168:00	X	X	X			
C1D15[h]		336:00	X	X	X	X		
C2D1	Predose[f]	00:00	X	X	X		X	
C3D1	Predose[f]	00:00	X	X	X		X	
EOT/Unscheduled/ Progression	EOT			X	X	X	X	

Abbreviations: C = Cycle; D = Day; EOT = end of treatment; FFPE = formalin-fixed, paraffin-embedded; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; RNA = ribonucleic acid; RO = receptor occupancy; TCR = T cell receptor.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Separate samples will be collected for blood RNA and blood RO assessments from all subjects. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[b] Separate samples will be collected for PBMC, blood multiparameter flow, serum factors, and plasma assessments. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[c] Mandatory predose and on-treatment biopsies for all subjects. Additional subjects may be added in the event that some subjects do not have obtainable tumor at the on-treatment time point.. Subjects obtaining biopsies should have adequate tissue collected as outlined in the laboratory manual. Additional optional biopsies may be collected at EOT, time of disease progression, or during another clinically meaningful event (eg, response or adverse event).

[d] Blood genotype sample to be collected at screening only.

[e] All subjects may provide an archived tumor specimen. Archival FFPE block or a minimum of 15 slides is required; 25 slides are preferred. See laboratory manual

[f] Predose: All predose samples for combinations should be taken prior to the start of the first infusion.

[g] D8 sample may be taken during D7 to D9 of a cycle.

[h] D15 sample may be taken during D12 to D18 of a cycle.

Table 5.6-4: Pharmacodynamic and Exploratory Biomarker Sampling Schedule for BMS-986178 Combination Therapy - Part 7 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with NSCLC)

Study Day of Sample Collection (1 Cycle = 6 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	Blood RNA, Blood RO[a]	Blood PD	PBMC, Blood Multiparameter Flow, Serum Factors, Plasma[b]	Tumor Biopsy[c] Section 5.6	Blood Genotype,[d] Blood TCR	Archived Tumor[e]
Screening				X		X	X	X
C1D1	Predose[f]	00:00	X	X	X			
C1D2		24:00			X			
C1D8[g]		168:00	X	X	X			
C1D15[h]	Predose[f]	00:00	X	X	X	X		
C1D29[i]	Predose[f]	00:00	X	X	X			
C2D1	Predose[f]	00:00	X	X	X		X	
C3D1	Predose[f]	00:00		X	X		X	
EOT/Unscheduled/ Progression	EOT			X	X	X	X	

Abbreviations: C = Cycle; D = Day; EOT = end of treatment; FFPE = formalin-fixed, paraffin-embedded; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; RNA = ribonucleic acid; RO = receptor occupancy; TCR = T cell receptor.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Separate samples will be collected for blood RNA and blood RO assessments. Blood RNA samples will be collected from all subjects. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[b] Separate samples will be collected for PBMC, blood multiparameter flow, serum factors, and plasma assessments. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[c] Mandatory predose and on-treatment biopsies for all subjects. Additional subjects may be added in the event that some subjects do not have obtainable tumor at the on-treatment time point. Subjects obtaining biopsies should have adequate tissue collected as outlined in the laboratory manual. Additional optional biopsies may be collected at EOT, time of disease progression, or during another clinically meaningful event (eg, response or adverse event).

[d] Blood genotype sample to be collected at screening only.

[e] All subjects may provide an archived tumor specimen. Archival FFPE block or a minimum of 15 slides is required; 25 slides are preferred. See laboratory manual.

[f] Predose: All predose samples for combinations should be taken prior to the start of the first infusion.

[g] D8 sample may be taken during D7 to D9 of a cycle.

[h] D15 sample may be taken during D13 to D17 of a cycle.

[i] D29 sample may be taken during D26 to D30 of a cycle.

Table 5.6-5 Pharmacodynamic and Exploratory Biomarker Sampling Schedule for BMS-986178 Combination Therapy - Part 8 (CA012004 - q12w Dosing)

Study Day of Sample Collection (1 Cycle = 12 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	Blood RNA, Blood RO[a]	Blood PD	PBMC, Blood Multiparameter Flow, Serum Factors, Plasma[b]	Plasma for ctDNA[j]	Tumor Biopsy[c], Section 5.6	Blood Genotype, Blood TCR[d]	Archived Tumor[e]
Screening				X			X	X	X
C1D1	Predose[f]	00:00	X	X	X	X			
C1D8[g]		168:00	X	X	X				
C1D15[h]		336:00	X	X	X	X	X		
C1D29[i]		672:00	X	X	X	X			
C1D78		1848:00[k]	X	X	X		X		
C2D1	Predose[f]	00:00	X	X	X	X		X	
C2D8[g]		168:00	X	X	X				
C2D15[h]		336:00	X	X	X	X			
C2D29[i]		672:00	X	X	X	X			
C3D1	Predose[f]	00:00	X	X	X	X		X	
C3D8[g]		168:00	X	X	X				
EOT/Unscheduled/ Progression	EOT		X	X	X	X	X	X	

Abbreviations: C = Cycle; D = Day; EOT = end of treatment; FFPE = formalin-fixed, paraffin-embedded; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; RNA = ribonucleic acid; RO = receptor occupancy; TCR = T-cell receptor.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Separate samples will be collected for blood RNA and blood RO assessments. Blood RNA samples will be collected from all subjects. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[b] Separate samples will be collected for PBMC, blood multiparameter flow, serum factors, and plasma assessments. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[c] Mandatory predose and on-treatment biopsies for all subjects. Additional subjects may be added in the event that some subjects do not have obtainable tumor at the on-treatment time point. Subjects obtaining biopsies should have adequate tissue collected as outlined in the laboratory manual. Additional optional biopsies may be collected at EOT, time of disease progression, or during another clinically meaningful event (eg, response or adverse event).

[d] Blood genotype sample to be collected at screening only.

[e] All subjects may provide an archived tumor specimen. Archival FFPE block or a minimum of 15 slides is required; 25 slides are preferred. See laboratory manual.

[f] Predose: All predose samples for combinations should be taken prior to the start of the first infusion.

[g] D8 sample may be taken during D7 to D9 of a cycle.

[h] D15 sample may be taken during D13 to D17 of a cycle.

[i] D29 sample may be taken during D26 to D30 of a cycle.

[j] Blood samples to be collected in 2x 9ml Streck tubes.

[k] C1D78 sample may be taken during D71 to D85.

[redacted]

5.8 Outcomes Research Assessments

Not applicable.

[redacted]

[redacted]

5.10 Additional Research Collection

Additional research collections and retention are mandatory for all subjects, except where prohibited by local laws or regulations.

This protocol will include residual samples for additional research (AR).

This collection for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and the advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

Sample Collection and Storage

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

- Additionally, residual blood (or blood derivatives such as serum, plasma, PBMCs and extracted RNA/DNA) or tumor tissue (archival or fresh biopsy and extracted RNA/DNA) (see Table 5.10-1) will also be retained for additional research purposes.
- Samples will be securely stored by the BMS Biorepository in New Jersey or at a BMS approved third party storage management facility.
- Samples will be stored in a coded fashion; and no researcher will have access to the key, which is securely held at the clinical site, so that there is no direct ability for a researcher to connect a sample to a specific individual.
- Additional research samples will be retained for 15 years or the maximum allowed by applicable law. No additional sampling is required for residual collections.

Further details of sample collection and processing will be provided to the site in the procedure manual.

Table 5.10-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time Points for which residual samples will be retained
PK	All
Archived Tumor Block or Slides	Pre-treatment
Fresh Tumor Biopsy	Pre-treatment, on-treatment and/or unscheduled/EOT
PBMC's	All
Serum	All
Plasma	All

Table 5.10-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time Points for which residual samples will be retained
Blood RNA	All
Blood Genotype/Blood TCR	All

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is no clear alternative cause for the AE that can be identified other than study treatment (e.g. disease progression, environmental causes, unrelated trauma).

Not related: There is a clear alternative cause identified for the AE other than study treatment.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

6.1 Serious Adverse Events

An ***SAE*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples

of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (See Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS or designee within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the electronic case report form (eCRF). The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious AE*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug until 100 days after discontinuation of dosing. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (electronic) as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

The investigator must immediately notify the BMS Medical Monitor or designee of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome, and where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

6.6 Potential Drug-Induced Liver Injury

Specific criteria for identifying pDILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a pDILI event. All occurrences of pDILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

pDILI is defined as:

1) Aminotransaminases (AT) (ALT or AST) elevation > 3 times ULN
   AND
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum ALP),
   AND
3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a pDILI event. All occurrences of pDILIs meeting the defined criteria must be reported as SAEs (see Section 6.1.1 for reporting details).

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, ECG, x-ray filming, or any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

8.1.1 Dose Escalation

As a Phase 1 dose escalation trial, the sample size for each dose escalation cohort depends on observed toxicity and posterior inference. Approximately 30 subjects are expected to be treated during each dose escalation part (BMS-986178 monotherapy [Part 1A], BMS-986178 in combination with nivolumab [Part 2A], and BMS-986178 in combination with ipilimumab [Part 3A]) for a combined total of approximately 90 subjects in Parts 1A, 2A and 3A. Initially, approximately 3 subjects will be treated at the starting dose levels of BMS-986178 or BMS-986178 in combination with nivolumab or ipilimumab. Additional cohorts of approximately 3 evaluable subjects will be treated at recommended dose levels per BLRM (-Copula) recommendations during the dose escalation phase. At least 6 DLT-evaluable subjects will be

treated at the MTD. At most, 12 DLT-evaluable subjects will be treated at each dose level. This limit is set to avoid instances in which the model could recommend adding subjects indefinitely to a specific dose level due to uncertainty in the tolerability profile. Escalation by more than 1 dose level (dose skipping) is not permitted.

As in any dose escalation study, the exact number of subjects in the dose escalation cannot be predicted. However, different estimates with the pre-specified parameters of the dose escalation design under various scenarios are provided (see Appendix 1). A maximum of 30 subjects is pre-specified as one of the simulation parameters (assuming approximately 6 subjects per dose level). The simulation provided in Appendix 1 uses combination therapy as an illustration (containing 5 dose levels for BMS-986178 and a fixed dose level for nivolumab [240 mg]). The simulation estimated a total of 15 to 21 subjects on average under different scenarios. Note the following difference between simulation setting and the conduct of the actual trial: 1) dose skipping is allowed in the simulation setting whereas in the actual clinical trial, dose skipping is not permitted, 2) the clinical team can override BLRM (-Copula) dose recommendation based on the totality of data (clinical safety data along with available PK and PD data). Based on these factors, there may be more subjects in the dose escalation phase than the number estimated in the simulation. For planning purposes, it is assumed that approximately 30 subjects may be treated in each dose escalation part.

8.1.2 Cohort Expansion

The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and PD information regarding BMS-986178 alone or in combination with nivolumab and/or ipilimumab.

In general, the estimated sample size for Parts 2B, 2C, 2D, 3B, 6B, and 7B in expansion phase is guided by Simon 2-stage design, which is based on target response rates (target ORR) and the ability to identify a signal for such clinical response that is above the SOC (historical ORR). Enrollment of subjects at the end of Stage 1 will continue while the initial efficacy evaluation is ongoing. Decisions regarding continuing or not continuing enrollment of a specific arm will be based on a combination of model guidance, clinical judgment on the totality of data (clinical safety, PK, PD, and efficacy), and communication between the Sponsor and investigators. Parts 2E and 3C include tumors from dose escalation for signal seeking. Due to the heterogeneity of response rates of the mixed tumors, approximately 40 subjects is assigned for each part (Part 2E and Part 3C). It is not the intent of the study to use Simon 2-stage design for formal hypothesis testing for the following reasons:

- At an early stage, the Sponsor would like to explore primary anti-tumor activity as a proof of confidence. According to the exploratory nature of an early phase design, the sample size is not large enough to clearly define the patient population. Meanwhile, there are no control arms planned as a comparison.
- In immuno-oncology, it is known that response rate alone does not reflect all potential clinical benefits. Factors such as duration of response, the depth of response, and delayed response could become evident as potential benefits according to the nature of immunotherapy.

- Safety is still the primary objective of the study, and if there is evidence of accumulated toxicity for a dose cohort, the cohort may be discontinued.

The Simon 2-stage design will be used as a guide for the disease-restricted expansion cohorts in Parts 2B, 2C, 2D, 3B, 6B, and 7B.[153,155] The total sample size for each expansion cohort will be calculated to provide a reasonable false-positive rate (FPR) and false-negative rate (FNR) based on assumptions of true (target) and historic ORR for each indication. The sample size and operating characteristics of the Simon 2-stage design are provided in Table 8.1.2-1, although this is not used for hypothesis testing. Approximately 12 subjects for CRC and OCs, 10 subjects for BC, 17 subjects for cervical cancer, and 28 subjects for RCC and NSCLC will be treated in Stage 1 for an initial evaluation of efficacy. This will inform potential early decisions and guide planning/operations or early termination after taking into consideration additional data, (eg, duration of response and/or SD and safety). If the true response rate is 10% for CRC and OC, the study has a 66% probability of early termination of the cohort. If the true response rate is 25% for BC, the study has a 53% probability of early termination of the cohort. If the true response rate is 20% for cervical cancer, the study has a 55% probability of early termination of the cohort. If the true response rate is 40% for RCC and NSCLC, the study has a 55% probability of early termination of the cohorts.

For an expansion cohort of 35 subjects in CRC and OC and the assumed true response rate of 30%, there is a 94% chance of observing at least 7 responses (in other words, the FNR is 6%). If the true response rate is only 10% rather than 30%, then there is a 6% chance that there will be at least 7 responses in 35 subjects (in other words, FPR is 6%). Also, if 7 responses are observed (eg, 20% observed response rate), the lower bound of the 80% CI for the ORR is 11% (higher than historical ORR of 10%). The CI is calculated using Clopper-Pearson method.

For an expansion cohort of 27 subjects with BC and the assumed true response rate of 50%, there is an 88% chance of observing at least 11 responses (in other words, the FNR is 12%). If the true response rate is only 25% rather than 50%, then there is a 5% chance that there will be at least 11 responses in 27 subjects (in other words, FPR is 5%). If 11 responses are observed (eg, 41% observed response rate), the lower limit of the 80% CI for the ORR is 28% (higher than historical ORR of 25%). The CI is calculated using Clopper-Pearson method.

For an expansion cohort of 37 subjects with cervical cancer and the assumed true response rate of 40%, there is an 87% chance of observing at least 12 responses (in other words, the FNR is 13%). If the true response rate is only 20% rather than 40%, then there is a 5% chance that there will be at least 12 responses in 37 subjects (in other words, FPR is 5%). If 12 responses are observed (eg, 32% observed response rate), the lower limit of the 80% CI for the ORR is 22% (higher than historical ORR of 20%). The CI is calculated using Clopper-Pearson method.

Table 8.1.2-1: Dose Expansion - Characteristics of the Simon 2-Stage Design[158]

Expansion Cohort	Historic ORR (%)	Target ORR (%)	Stage 1/ Total N	Stage 1 Responses Futility Boundary	FPR/1-FNR (%)	Probability of Early Stopping (%)
CRC, Ovarian Cancer	10	30	12/35	1	10/90	66
Bladder Cancer	25	50	10/27	2	10/90	53
Cervical Cancer	20	40	17/37	3	10/90	55
NSCLC, RCC	40	60	28/41	11	10/90	55

Abbreviations: CRC = colorectal cancer; FNR = false-negative rate; FPR = false-positive rate.

The number of subjects receiving treatment for efficacy evaluation is approximate, and additional subjects may be treated in order to have sufficient response-evaluable subjects per expansion cohort.

8.1.3 Schedule and Dose Exploration and Safety Exploration

The purpose of Parts 4, 5, 6A, 7A, and 8 is to assess safety, tolerability, preliminary efficacy, PK, and PD information of BMS-986178 in combination with nivolumab administered with a less frequent dosing schedule (q4w Part 4 and q12w Part 8 for BMS-986178) or BMS-986178 in combination with higher dose of ipilimumab (Part 5) or BMS-986178 in combination with nivolumab and ipilimumab (Parts 6A and 7A). A minimum of 6 subjects will be treated at the MTD/RP2D chosen from Part 2A or Part 3A. Up to 12 subjects may be treated for further evaluation of safety, PK, or PD parameters. Administration of BMS-986178 in combination with nivolumab and/or ipilimumab in 6 to 12 subjects per dose and schedule level provides 90% probability of observing at least 1 occurrence of a specific AE that would occur with a 32% or 17% incidence in the population, respectively. Furthermore, 6 to 12 subjects provide some precision of PD biomarker effect estimation. To assess the PD effects, pre-treatment and on-treatment whole blood and serum samples and tumor biopsies will be required. It is of interest to ensure the precision of the estimate of the ratio of on-treatment biomarker assessments to pre-treatment (baseline) levels. Assuming that a biomarker is measured as a continuous variable, a given number of subjects will provide the confidence that the estimate of the ratio of on-treatment to baseline values will be within 20% of the true value, as shown in Table 8.1.3-1.

Table 8.1.3-1: Probability that Estimated Ratio of On-treatment to Pre-treatment (Baseline) Value is Within 20% of True Value

Intra-subject Standard Deviation (Log-scale)		0.2	0.3	0.4	0.5	0.6	0.7	0.8
Probability	N = 6	92%	76%	62%	52%	44%	38%	34%
	N = 12	99%	90%	78%	68%	59%	52%	46%

For example, for a biomarker (eg, activated and memory CD4 and CD8 T-cells) with an intra-subject standard deviation of 0.5, if the true ratio of post-baseline to baseline geometric means is 1.2 (increase from baseline is 20%), there is 68% probability that the estimated ratio would be within 0.96 and 1.44 (or a percent change between -4% and 44%) with 12 subjects per treatment arm. If the true increase from baseline is 60%, for a biomarker with the same variability, then there is 68% probability that the estimated percent change would be between 28% and 92% with 12 subjects per treatment arm.

Up to approximately 20 evaluable subjects per dose cohort will be treated in Part 8. This sample size provides a 90% CI for the true proportion of subjects showing a change in receptor occupancy with width of 37% and 26% respectively when the observed proportion of subjects showing a change in receptor occupancy is 70% and 90%, as shown in Table 8.1.3-2. The maximum width of all 90% CIs is 40% and the maximum margin of error is 21% with a sample size of 20 per cohort.

Table 8.1.3-2: 90% Confidence Interval for the True Proportion of Subjects Showing a Biomarker Change

n	# subjects showing the trend	90% CI
20	14	(49%, 86%)
	18	(72%, 98%)

8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who signed an ICF and are registered into the IRT.
- All Treated Subjects: All subjects who received at least 1 dose of study medication.
- The PK data set includes all available concentration-time data from subjects who received any BMS-986178, nivolumab, or ipilimumab.
- The immunogenicity data set consists of all available immunogenicity data from subjects who received BMS-986178, nivolumab, or ipilimumab.
- The biomarker data set includes all available biomarker data from subjects who received any study drug(s).
- Response-evaluable subjects: All treated subjects with measurable disease and any of the following: 1) at least 1 post-baseline tumor measurement , 2) clinical progression, or 3) death.

Analyses of safety, extent of exposure, biomarkers, PK, preliminary efficacy, immunogenicity, and PD will be based on all treated subjects.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The assessment of safety will be based on the incidence of AEs, SAEs, AEs leading to discontinuation, and deaths. In addition, clinical laboratory test abnormalities will be examined.

AEs and laboratory values will be graded according to NCI CTCAE v4.03.

8.3.2 Secondary Endpoint(s)

8.3.2.1 Efficacy

The anti-tumor activity of BMS-986178 alone or in combination with nivolumab and/or ipilimumab will be measured by ORR, duration of response, and PFSR at 24 weeks based on RECIST v1.1. The above will be determined based on tumor measurements occurring at baseline, every 8 weeks (± 1 week) during the treatment period. and every 12 weeks during the Survival Follow-up Period.

- Best overall response (BOR) is assessed by investigator and/or BICR per RECIST 1.1 criteria.
- ORR is defined as the proportion of all treated subjects whose BOR is either CR or PR.
- Duration of response, computed for all treated subjects with a BOR of CR or PR, is defined as the time between the date of first response and the date of disease progression or death, whichever occurs first.
- PFSR at 24 weeks is defined as the proportion of treated subjects remaining progression free and surviving at 24 weeks. The proportion will be calculated by the Kaplan-Meier estimate, which takes into account censored data

8.3.2.2 Pharmacokinetics

Selected BMS-986178 parameters, such as Cmax, Tmax, AUC(0-t), and AUC(TAU), will be assessed in 2 cycles depending on the schedule for monotherapy or in combination with nivolumab and/or ipilimumab. Parameters such as Ctau, CLT, Css-avg, accumulation index (AI), and effective elimination half-life (T-HALFeff) will be assessed in the second cycle when intensive PK are collected. A separate listing, summary, and plot will be generated for Ctrough.

8.3.2.3 Immunogenicity

The secondary objective of immunogenicity will be assessed by the frequency of positive ADA to BMS-986178 or nivolumab or ipilimumab.

8.3.2.4 Pharmacodynamics

The secondary objective of pharmacodynamics will be assessed by the proportion of subjects showing a change in pharmacodynamic biomarkers such as soluble OX40 and peripheral OX40 receptor occupancy along with tumor pharmacodynamic of BMS-986178 in combination with nivolumab or nivolumab monotherapy (Part 8).

[redacted]

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated. Summary statistics for age, body weight, and height will be tabulated.

8.4.2 Efficacy Analyses

The primary efficacy analyses will be performed on all treated subjects. Efficacy analyses based on response-evaluable subjects may be performed for interim analyses when the minimum follow-up period is less than sufficient to warrant adequate interpretation of results. Listing of tumor measurements will be provided by subject and study day in each arm and dose level. Individual subject's BOR will be listed based on RECIST 1.1.

To describe the anti-tumor activity of BMS-986178 alone or in combination with nivolumab and/or ipilimumab, ORR will be calculated. ORR and corresponding two-sided exact 95% CI by the Clopper-Pearson method will be provided by treatment and/or dose level and tumor type. Median duration of response and corresponding two-sided 95% CI will be reported by treatment and/or dose level and tumor type. Duration of response will be analyzed using the Kaplan-Meier method.

In addition, PFSR, the probability of a subject remaining progression free or surviving to 24 weeks, will be estimated by the Kaplan-Meier methodology by treatment, tumor type, and dose level. The corresponding 95% CI will be derived based on Greenwood formula.

[redacted]

8.4.3 Safety Analyses

All recorded AEs will be listed and tabulated by system organ class, preferred term, and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator, and abnormalities, if present, will be listed

8.4.4 Pharmacokinetic Analyses

All individual PK parameters will be listed for each analyte, including any exclusions and reasons for exclusion from summaries. Summary statistics will be tabulated for each PK parameter by treatment. Geometric means and coefficients of variation will be presented for Cmax, AUC(0-t),

AUC(TAU), Ctau, CLT, Css-avg, and AI. Medians and ranges will be presented for Tmax. Medians and ranges will be presented for Tmax. Means and standard deviations will be presented for all other PK parameters (eg, T-HALFeff).

BMS-986178 dose dependency will be assessed in dose escalation monotherapy. To describe the dependency on dose of BMS-986178, scatter plots of Cmax, AUC(0-t), and AUC(TAU) versus dose may be provided at the cycles when these PK parameters are assessed, as specified in Section 5.5. Exploratory assessments of dose proportionality based on a power model with CI around the power coefficient may be performed. Nivolumab and ipilimumab EOI and trough (Ctrough) concentrations and BMS-986178 trough concentration will be tabulated by treatment and study day using summary statistics. These data may also be pooled with other datasets for population PK analysis, which will be presented in a separate report.

8.4.5 Biomarker Analyses

In Part 8, summary statistics for the proportion of subjects showing a change in pharmacodynamics biomarkers will be tabulated by treatment cohort.

[redacted]

8.4.7 Outcomes Research Analyses

Not applicable.

8.4.8 Other Analyses

A listing of all available immunogenicity data will be provided by treatment, dose, and immunogenicity status. The frequency of subjects with positive ADA assessment of BMS-986178, nivolumab, and ipilimumab will be summarized.

8.5 Interim Analyses

Administrative interim analysis for internal decision making or external publication purpose may be performed. No formal inferences requiring any adjustment to statistical significance level will be performed.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable

opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to BMS.

9.1.2.1 Source Documentation

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, AE tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

BMS will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study and BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product. Records or logs must comply with applicable regulations and guidelines and should include:

- Amount received and placed in storage area
- Amount currently in storage area
- Label identification number or batch number
- Amount dispensed to and returned by each subject, including unique subject identifiers
- Amount transferred to another area/site for dispensing or storage
- Nonstudy disposition (eg, lost, wasted)
- Amount destroyed at study site, if applicable
- Amount returned to BMS
- Retained samples for bioavailability/bioequivalence, if applicable
- Dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents, or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS EDC tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the or electronic SAE form and Pregnancy Surveillance form, respectively. If an electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS EDC tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS EDC tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any

event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.
Additional Research	Those scientific activities which cannot be reasonably anticipated at the time of trial design, for which we would like to collect and/or retain samples from study subjects. Examples of additional research include, but are not limited to, new assay development and validation, companion diagnostic development, new hypotheses in the interaction of drug and the human body, and exploration of emerging science in the understanding of disease.

11 LIST OF ABBREVIATIONS

Term	Definition
5-FU	5-fluorouracil
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AFP	alpha fetal protein
AI	accumulation index
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APC	antigen-presenting cell
AST	aspartate aminotransferase
AT	Aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-t)	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in 1 dosing interval
BC	bladder cancer
BCR	B-cell receptor
BICR	Blinded Independent Central Review
BLA	Biologics License Application
BLRM	Bayesian Logistic Regression Method
BMS	Bristol-Myers Squibb
BOR	best overall response
BSC	best supportive care
BUN	blood urea nitrogen
C	Cycle
C12	concentration at 12 hours

Term	Definition
CEA	carcinoembryonic antigen
Cavgss	steady-state time-averaged concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CrCL	creatinine clearance
CLT	total body clearance
Cmax	maximum observed concentration
Cmaxss	steady-state peak concentration
CMI	cell-mediated immunity
Cminss	steady-state trough concentration
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRF	case report form, paper or electronic
CRP	C-reactive protein
Css-avg	average concentration over a dosing interval (AUC[TAU]/tau)
CT	computed tomography
CTA	clinical trial agreement
Ctau	the observed concentration at the end of a dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte associated antigen-4
Ctrough	Trough observed plasma concentration
D	Day
CV	coefficient of variation
DEHP	diethylhexyl phthalate
DLT	dose-limiting toxicity
EC_{50}	half maximal effective concentration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Term	Definition
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOI	end of infusion
EOT	end of treatment
EWOC	escalation with overdose control
Fc	fragment crystallizable
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	formalin-fixed, paraffin-embedded
FIH	first-in-human
FNR	false-negative rate
FPR	false-positive rate
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
Geo Mean	geometric mean
GGT	gamma-glutamyl transferase
gMDSC	granulocytic myeloid-derived suppressor cell
GITR	glucocorticoid-induced TNFR-related gene
hCG	human chorionic gonadotrophin
hERG	human Ether-à-go-go-Related Gene (hERG)
HIV	human immunodeficiency virus
HPV	human papillomavirus
HRT	hormone replacement therapy
IASLC	International Association for the Study of Lung Cancer
IB	Investigator Brochure
ICD	International Classification of Diseases
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

Term	Definition
IFN-γ	interferon-γ
IgG1	immunoglobulin G1
IgG2	immunoglobulin G2
IHC	Immunohistochemistry
IMDC	International Metastatic RCC Database Consortium
IMP	investigational medicinal products
IL	Interleukin
IO	immuno-oncology
IP	Intraperitoneal
IRB	Institutional Review Board
IRR	infusion-related reaction
IUD	intrauterine device
IV	Intravenous
IRT	Interactive Response Technology
KPS	Karnofsky Performance Scale
LDH	lactic acid dehydrogenase
LFT	liver function test
mAb	monoclonal antibody
MABEL	minimal anticipated biologic effect level
mCRC	metastatic colorectal cancer
MC38	murine colon carcinoma cell line 38
MDSC	myeloid-derived suppressor cell
mOS	median overall survival
mPFS	median progression free survival
mRCC	metastatic renal cell carcinoma
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSKCC	Memorial Sloan-Kettering Cancer Center
MST	Medical Surveillance Team

Term	Definition
MTD	maximum tolerated dose
N	number of subjects or observations
NCA	non-compartmental analysis
NCI	National Cancer Institute
NK	natural killer
NKT	natural killer T
NSCLC	non-small cell lung cancer
OC	ovarian cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PBT	platinum-based therapy
PCR	polymerase chain reaction
PD	Pharmacodynamics
PD-1	programmed cell death-1
pDILI	potential drug-induced liver injury
PET	positron emission tomography
PFS	progression free survival
PFSR	progression free survival rate
PK	Pharmacokinetics
PR	partial response
PSA	prostate-specific antigen
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
q6w	every 6 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RO	receptor occupancy

Term	Definition
RP2D	recommended Phase 2 dose (s)
RT-qPCR	real-time quantitative PCR
SAE	serious adverse event
SD	stable disease
SNP	single-nucleotide polymorphism
SOC	standard of care
T	Time
T3	triiodothyronine
T4	Thyroxine
TCGA	The Cancer Genome Atlas
TCR	T-cell receptor
TF	tumor free
TGI	tumor growth inhibition
TIL	tumor-infiltrating lymphocyte
T-HALF	half life
T-HALFeff	effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure (exposure measure includes AUC[TAU], Cmax and Ctau)
Tmax	time of maximum observed concentration
TNF-α	tumor necrosis factor-α
TNFRsf	tumor necrosis factor receptor super family
Treg	regulatory T-cell
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
Vc	volume of central
VEGF	vascular endothelial growth factor
VS	vital signs
Vss	volume of distribution at steady state
Vz	volume of distribution of terminal phase (if IV and if multi-exponential decline)
WOCBP	women of childbearing potential

APPENDIX 3 RECIST 1.1

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least 1 measurable tumor lesion. When computed tomographic (CT) scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

Central assessments may be planned for this study. Copies of all scans should be kept at the site as part of the subject study file. At the Sponsor's discretion, scans may be collected centrally for further analysis.

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1 Measurable Lesions

Measurable lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT/magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- *Malignant lymph nodes*: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥ 15 mm in the ***short*** axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow-up, only the ***short*** axis will be measured and followed.

1.2 Non-Measurable Lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions
- Lesions considered truly non-measurable include the following: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of the skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by reproducible imaging techniques

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone Lesions

- Bone scan, positron emission tomography (PET) scan or plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components* that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.3.2 Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

1.3.3 Lesions with Prior Local Treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

1.4 Specifications by Methods of Measurements

1.4.1 Measurement of Lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 30 days before the beginning of the treatment.

1.4.2 Method of Assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

1.4.2.1 CT/MRI Scan

CT/MRI is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT/MRI scan is based on the assumption that CT/MRI slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

1.4.2.2 Chest X-ray

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

1.4.2.3 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

1.4.2.4 Ultrasound

Ultrasound is ***not*** useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

1.4.2.5 Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is ***not*** advised.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

2.1 Target Lesions

When more than 1 measurable lesion is present at baseline all lesions up to **a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as *target lesions*** and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their **size** (lesions with the longest diameter), should be representative of all involved organs, and should lend themselves to ***reproducible repeated measurements***.

A ***sum of the diameters*** (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the ***baseline sum diameters***. If lymph nodes are to be included in the sum, then as noted below, only the ***short*** axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

2.1.1 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of**

≥ 15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

2.2 Non-Target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as **'present'**, **'absent'**, or in rare cases **'unequivocal progression'**. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION

3.1 Evaluation of Target Lesions

Complete Response (CR): **Disappearance of all target lesions.** Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a **30% decrease in the sum of diameters of target lesions**, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a **20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study*** (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an **absolute increase of at least 5 mm**. (*Note:* The appearance of 1 or more new lesions is also considered progression.)

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

3.1.1.2 Target Lesions That Become 'Too Small to Measure'

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5-mm CT slice thickness (but should not be changed with varying CT slice thickness).

3.1.1.3 Target Lesions That Split or Coalesce on Treatment

- When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.
- As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

3.2 Evaluation of Non-Target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) above the normal limits.

Progressive Disease (PD): *Unequivocal progression* of existing non-target lesions. (*Note:* The appearance of 1 or more new lesions is also considered progression.)

3.2.1 Special Notes on Assessment of Non-Target Lesions

The concept of progression of non-target disease requires additional explanation as follows:

3.2.1.1 When the Subject Also Has Measurable Disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

3.2.1.2 When the Subject Has Only Non-Measurable Disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

- A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable), a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: that is, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localized to widespread or may be described in protocols as 'sufficient to require a change in therapy'.
- If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point.

3.2.1.3 Tumor Markers

Tumor markers *alone* cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a subject to be considered as having attained a complete response.

3.3 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: that is, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (eg, some 'new' bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered that reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. *If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.*

3.3.1 FDG-PET Evaluation

While [^{18}F] fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of the qualitative assessment of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial positive FDG-PET scan).
  - If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

4 RESPONSE CRITERIA

4.1 Timepoint Response

A response assessment should occur at each timepoint specified in the protocol.

For subjects who have **measurable disease** at baseline Table 4.1-1 provides a summary of the overall response status calculation at each timepoint.

Table 4.1-1: Timepoint Response: Subjects with Target (+/– Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD

Table 4.1-1: Timepoint Response: Subjects with Target (+/– Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE =not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the subject is **not evaluable (NE)** at that timepoint. If only a subset of lesion measurements are made at an assessment, the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned timepoint response.

4.1.1 Confirmation Scans

- **Verification of Response:** *Confirmation of PR and CR is required after at least 4 weeks following initial assessment to ensure responses identified are not the result of measurement error.*

4.2 Best Overall Response: All Timepoints

The *best overall response* is determined once all the data for the subject are known. It is the best response recorded from the start of the study treatment until the date of objectively documented progression based on RECIST v1.1, taking into account any requirement for confirmation, or the date of subsequent anti-cancer therapy, whichever occurs first in the study. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Best response is defined as the best response across all timepoints with subsequent confirmation. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent timepoint as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 4.2-1. When SD is believed to be best response, it must meet the protocol specified minimum time from baseline. Measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6 to 8 weeks) that is defined in the study protocol.

Table 4.2-1: Best Overall Response When Confirmation of CR and PR Is Required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since the disease must have reappeared after CR). The best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.3 Duration of Response

4.3.1 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.3.2 Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

APPENDIX 4 ECOG PERFORMANCE STATUS

ECOG Performance Status[a]	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities Up and about more than 50% of waking hours
3	Capable of only limited self-care Confined to bed or chair more than 50% of waking hours
4	Completely disabled Cannot carry on any self-care Totally confined to bed or chair
5	Dead

[redacted]

APPENDIX 5 INTERNATIONAL METASTATIC RCC DATABASE CONSORTIUM (IMDC) PROGNOSTIC CRITERIA

Adverse Prognostic Factors
Clinical
KPS < 80%
Time from diagnosis to treatment < 1 year
Laboratory
Hemoglobin < LLN
Corrected calcium > ULN
Absolute neutrophil count > ULN
Platelet count > ULN

LLN = Lower limit of normal
ULN = Upper limit of normal

Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 (4.0 - serum albumin [g/dL]), where 4.0 represents the average albumin level in g/dL.

Corrected calcium (mmol/L) = measured total Ca (mmol/L) + 0.02 (40 - serum albumin [g/L]), where 40 represents the average albumin level in g/L

Risk Group Based on Number of Adverse Prognostic Factors	
Number of Adverse Prognostic Factors Present	**Risk Group**
0	Favorable
1-2	Intermediate
3-6	Poor

[redacted]

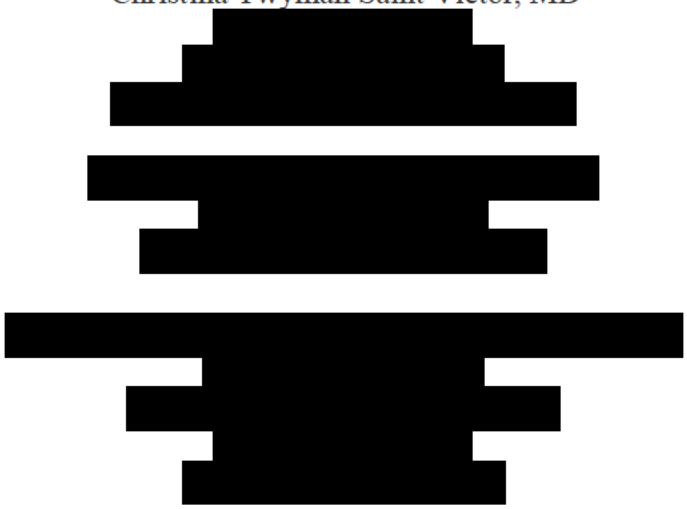
Protocol Number: CA012004
IND Number: 128376
EUDRACT Number 2015-004816-39
Date: 18-Feb-2016
Revised Date: 12-May-2021

CLINICAL PROTOCOL CA012004:

A Phase 1/2a Study of BMS-986178 Administered Alone or in Combination with Nivolumab and/or Ipilimumab in Subjects with Advanced Solid Tumors

Protocol Amendment Number: 04 Site Specific
Applicable to sites in the United States participating in Part 9

Study Director and Medical Monitor
Christina Twyman Saint Victor, MD



DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 04 Site-specific	12-May-2021	The purpose of this revision is to: • Allow the inclusion of prior anti-cancer therapy with PD-1/PD-L1 checkpoint inhibitor in line with recently approved treatments for TNBC. This increases the maximum allowable prior anti-cancer therapies from 1 to 2. • Extend the disease population to include ER-low positive breast cancer in line with ASCO/CAP updated guidelines to add the classification of ER-low positive tumors in Part 9. Other updates have been made to assess and mitigate the potential risks of acute SARS-CoV-2 infection, clarify prior and concurrent vaccine administration including authorized or approved SARS-CoV-2 vaccines, and to clarify on-treatment biopsy timing for Part 9. In addition, minor edits and corrections were made.
Revised Protocol 05c Site-specific	12-May-2020	Incorporated Administrative Letters 09 and 10 as well as the following: • Additional language for clarity regarding the vital signs timing and frequency, as well as DPV-001 storage, handling, preparation and administration details. • Update to statistical considerations • Typographical errors were corrected, and edits were made for consistency and clarity
Administrative Letter 10	04-Mar-2020	• The Medical Monitor / Study Director of the study is transitioned from [redacted] to [redacted], for Part 9 of the study effective March 16, 2020. [redacted] will complete the Part 1-8 CSR.
Administrative Letter 09 Specific	12-Feb-2020	[redacted] 3) **Page 132, Section "4. Study Drug", Table "4-1: Study Drugs for CA012004", in the box field of "Potency" of the "UbiLT3 and UbiLT6 vaccine":** *Previously written:* "1 mg/mL 0.6 mL/vial and as indicated in the Ubivac IB[52]"

Document	Date of Issue	Summary of Change
		Changed to: "1 mg/mL 0.7 mL/vial and as indicated in the Ubivac IB[52]"
Administrative Letter 08 Specific	27-Jan-2020	• Due to delay in Part 9, revprot05a was never implemented or distributed. Revprot05b is the updated version that has been distributed for HA/IRB review, and will be executed only at US sites 0002, 0007, 0017, 0019 and 0024.
Revised Protocol 05b Site-specific	26-Nov-2019	• Included all changes from Revised Protocol 05a • Updated introduction, study and dosing rationales, objectives, and schedule and dose exploration and safety exploration to reflect the addition of Part 9 • Clarified that Parts 1-8 have been completed • Updated subject treated numbers for BMS986178 and nivolumab based on most current IBs. • Added references to myocarditis based on most current nivolumab IB. • Removed Retreatment and Survival/Response FU visits for subjects in Part 1-9. • Defined maximum treatment duration. • Removed select PK/PD samples • Updated inclusion criteria for ER and PR for TNBC (Part 9) consistent with ASCO/CAP guidelines. • Updated criteria for complete abstinence. • Typographical errors were corrected, and edits were made for consistency and clarity
Revised Protocol 05a Site-specific	22-Jun-2018	• Incorporates DRibble vaccine (DPV-001) as a new combination with BMS 986178 in Part 9 • Update Schedule of assessments to incorporate Part 9 • Typographical errors were corrected, and edits were made for consistency and clarity
Revised Protocol 05	11-Dec-2017	Incorporates Administrative Letters 04, 05, 06, and 07 and the following: • Addition of Part 8 • Update of Appendix 1 • Update schedule of assessments • Update of address Typographical errors were corrected, and edits were made for consistency and clarity
Administrative Letter 07	19-Oct-2017	Clarify that if subjects continue for additional cycles, past cycle 4, all study drugs will continue for all cycles in Parts 7A and 7B in Sections 3.1.4.2 and 3.1.5.8 and acknowledge the ommission of the word 'Beyond' in Table 5.1-6
Administrative Letter 06	11-Jul-2017	Correction of typographical errors in Sections 5.1 and 5.5.1
Administrative Letter 05	03-May-2017	Correction of typographical error in Section 3.1.6

Document	Date of Issue	Summary of Change
Administrative Letter 04	02-May-2017	Correction of typographical error in Section 3.1.6
Revised Protocol 04	04-Apr-2017	Incorporates Amendment 04 and Administrative Letters 02 and 03
Amendment 04	04-Apr-2017	The amendment includes the following: • Addition of Parts 4, 5, 6, and 7 • Update of study title • [redacted] • [redacted] • Update of study design and study visit schematic • Update of inclusion and exclusion criteria to include the new parts and clarify the maximum number of prior treatments allowed • Update of study drug dosing and method of assigning subjects • Update of dose delay language and addition of criteria for resuming treatment in subjects with an infusion reaction • Update/addition of tables for treatment procedures, pharmacokinetic and anti-drug antibody sampling schedule, and pharmacodynamic/ biomarker sampling schedule • Update of sample size information to include the new parts • Update of Appendix 1 to include statistical methods for the new parts • Typographical errors were corrected, and edits were made for consistency and clarity.
Administrative Letter 03	16-Dec-2016	Change in Study Director/Medical Monitor address
Administrative Letter 02	12-Dec-2016	Correction of typographical error in Section 3.1.3.6, first paragraph, first sentence
Revised Protocol 03	23-Nov-2016	Incorporates Amendment 03 and Administrative Letter 01
Amendment 03	23-Nov-2016	The amendment includes the following: • Removal of Part 1B • Addition of Part 2D, 2E, 3C and Part 2A cohort dose -1 • Change to have imaging as central read • Add text to allow for intermediate and lower doses in escalation • Included text to add potentially more than 1 dose at RP2D • Updated versions numbers for current IB's. • Updating to the new PMD for WOCBP Section • Require fresh tumor biopsy from all subjects • Additional sample to be collected in combination cohorts for RO • Update to not require archived tumor biopsies • Updated Statistical Analysis section • Typographical errors were corrected, and clarifications were made for consistency.

Document	Date of Issue	Summary of Change
Administrative Letter 01	14-Jun-2016	Correction of typographical error in Section 3.3.1, inclusion criterion 10(g) and Table 5.1-1, Screening Procedure Outline, complete blood count (CBC) with differential
Revised Protocol 02	08-Jun-2016	Incorporates Amendment 02
Amendment 02	08-Jun-2016	The purpose of this amendment is to address comments received from Health Authorities. The amendment includes the following: • Change the definition for "Related AE's" and "Not Related AE's". • Update prior therapy inclusion criteria for dose escalation subjects. • Remove timeframe from hematologic DLT grade 3 febrile neutropenia. • Change to have CBC with differential processed through LLDS. • Add new model document language for Additional Research Collection and Imaging scans. • Typographical errors were corrected, and clarifications were made for consistency.
Revised Protocol 01	26-Apr-2016	Incorporates Amendment 01
Amendment 01	26-Apr-2016	The purpose of this amendment is to address comments received from Health Authorities. The amendment includes the following: • The timing of the initiation of combination therapy dose escalation cohorts was revised, a sentinel subject was added to all dose cohorts, Parts 1B and 2B were removed and the subsequent study parts were renamed (Part 1C to Part 1B, Part 2C to Part 2B, and Part 2D to Part 2C), DLT period across the study (28 days) was made uniform, the post-infusion observation period was extended to 4 hours, contraceptive requirements were updated, lipase and amylase ≤ 1.5×ULN were removed as criteria for adequate organ function, DLT criteria were revised, a timepoint was added for safety monitoring, the rationale for use of blood and tumor tissue in biomarker studies was clarified, prior therapy requirements for dose expansion cohorts were updated, and BLRM language was clarified. • Typographical errors were corrected, and clarifications were made for consistency.
Original Protocol	18-Feb-2016	Not applicable

[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04 SITE SPECIFIC

Section Number & Title	Description of Change	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Section 3.1.6.1, Screening Period; Section 5.1.1 Retesting During Screening	Added language to allow extension of screening period with active SARS-CoV-2 infection with medical monitor approval. Added screening eligibility related to active SARS-CoV-2 infection.	[redacted]
Section 3.3.1, Inclusion Criteria	Updated language of signed written informed consent, types of participant and target population, and age and reproductive status to align with current nivolumab program standards. Increased maximum prior anti-cancer therapies from 1 to 2 with the inclusion of prior PD-1/PD-L1 checkpoint inhibitor. Increased the window of vaccine administration.	[redacted]
Section 3.3.1, Inclusion Criteria; Section 3.3.2, Exclusion Criteria	Allow prior PD-1/PD-L1 checkpoint inhibitors. Updated history of allergy to nivolumab as an exclusion criterion to include Part 9 participants since it is now permitted.	[redacted]
Section 3.3.1, Inclusion Criteria; Section 3.4.1, Prohibited and/or Restricted Treatments	Allow prior endocrine therapy in ER-low positive participants. Added language to prohibit concurrent use of hormonal therapy for ER-low positive breast cancer subjects in Part 9.	[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04 SITE SPECIFIC		
Section Number & Title	**Description of Change**	[redacted]
Section 3.3.2, Exclusion Criteria	Added target disease exceptions for Part 9 regarding controlled CNS metastases to include radiographic stability of CNS lesions within 28 days. Updated timeframe for major surgery. Added pregnant and breast-feeding subjects to exclusion criteria. Added language to exclude active or uncontrolled infection, SARS-CoV-2 infection, and SARS-CoV-2 vaccination prior to initiation of study treatment with specified timeframe.	
Section 3.3.2, Exclusion Criteria; Section 3.4.1, Prohibited and/or Restricted Treatments	Updated washout period of cytotoxic agents, including investigational cytotoxic drugs.	
Section 3.4.1, Prohibited and/or Restricted Treatments	Added language to prohibit investigational SARS-CoV-2 vaccine and/or live/attenuated vaccines.	
Sections 3.4.3, Permitted Therapy	Updated to allow the treatment of active SARS-CoV-2 infections with investigational therapies. Updated vaccine administration from ≥ 14 days prior or after study treatment to ≥ 10 days prior or after study treatment.	
Section 4.5.4, Dose Delays due to Toxicity; Section 4.5.5.1 Criteria to Resume Treatment in Subjects with a Dose Delay	Added dose delays due to SARS-CoV-2 infection. Added language to continue tumor assessments and periodic study visit safety and laboratory assessments regardless of dose delays.	

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04 SITE SPECIFIC		
Section Number & Title	**Description of Change**	[redacted]
Table 5.1-1, Screening Procedural Outline Parts 1-9	Added to table notes when assessment(s) must be done for informed consent and inclusion/exclusion criteria.	
Table 5.1-8, On Treatment Procedural Outline Part 9	Added SARS-CoV-2 to Adverse Event Reporting requirements. Added doses for UbiLT3 and UbiLT6	
Table 5.1-9, Follow-up Procedural Outline Parts 1-9	Added to table notes the timing from treatment/cohort assignment to receiving first dose of study medication.	
Section 5.7.2.1, Tissue Biopsies from All Subjects	Added on-treatment biopsy timing for Part 9.	
Section 6, Adverse Events; Section 6.1.1, Serious Adverse Event Collection and Reporting	Updated to collect and follow all immune mediated AEs and AEs associated with SARS-CoV-2 infection to detect safety signal in study population or study treatment.	
Section 6.4, Pregnancy	Changed time of study exposure if pregnant from 5 half-lives to 1 year.	

SYNOPSIS

Clinical Protocol CA012004

Protocol Title: A Phase 1/2a Study of BMS-986178 Administered Alone or in Combination with Nivolumab and/or Ipilimumab in Subjects with Advanced Solid Tumors

Investigational Product(s), Dose and Mode of Administration, and Duration of Treatment with Investigational Product(s):

BMS-986178, an anti-OX40 agonist monoclonal antibody (mAb) supplied as a sterile 25-mg/mL formulation, is to be administered as an intravenous (IV) infusion alone or in combination with nivolumab and/or ipilimumab or DPV-001 per the cohort assignment and the duration of treatment, as indicated in the protocol. Nivolumab, an anti-programmed cell death-1 (PD-1) mAb, is available as a sterile 10-mg/mL formulation to be administered as an IV infusion. Ipilimumab, an anti-cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) mAb, is available as a sterile 5-mg/mL formulation to be administered as an IV infusion. DPV-001 is composed of two cell-free microvesicle vaccines, UbiLT3 and UbiLT6, developed from two cancer cell lines (UbiLT3 and UbiLT6 cell lines respectively). UbiLT3 was derived from a cancer of mixed histology (Squamous and adenocarcinoma) and UbiLT6 was developed from an adenocarcinoma. It is available as a sterile 1 mg/mL formulation to be administered as an intranodal (IN)/intradermal (ID) injection.

Study Phase: 1/2a

Research Hypothesis: It is anticipated that anti-OX40 agonist antibody (BMS-986178), administered as a single agent or in combination with anti-PD-1 mAb (nivolumab) or anti-CTLA-4 mAb (ipilimumab) or DPV-001, will demonstrate adequate safety and tolerability, as well as a favorable risk/benefit profile, to support further clinical testing. No prospective hypotheses are being formally evaluated.

Objectives:

Primary Objective:

The primary objective is to determine the safety, tolerability, dose-limiting toxicities (DLTs), and maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab or DPV-001 in subjects with advanced solid tumors.

Secondary Objectives:

Secondary Objectives for Parts 1-8

- To investigate the preliminary anti-tumor activity of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab in subjects with advanced solid tumors
- To characterize the pharmacokinetics (PK) of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab
- To characterize the immunogenicity of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab and the immunogenicity of nivolumab or ipilimumab administered with BMS-986178
- To assess the proportion of subjects showing a change in peripheral pharmacodynamic biomarkers such as soluble OX40 and peripheral OX40 receptor occupancy along with tumor pharmacodynamic of BMS-986178 in combination with nivolumab or nivolumab monotherapy (Part 8)

Secondary Objectives for Part 9

- To investigate the preliminary anti-tumor activity of BMS 986178 in combination with nivolumab and DPV-001 and nivolumab in combination with DPV-001 in subjects with triple negative breast cancer and estrogen receptor (ER)-low positive breast cancer
- To characterize the pharmacokinetics (PK) of BMS 986178 in combination with nivolumab and DPV-001

- To characterize the immunogenicity of BMS 986178 in combination with nivolumab and DPV-001
- To assess the proportion of subjects showing a change in peripheral or tumor pharmacodynamic biomarkers such as sustained T cell expansion with DPV-001 in combination with nivolumab with or without BMS-986178.

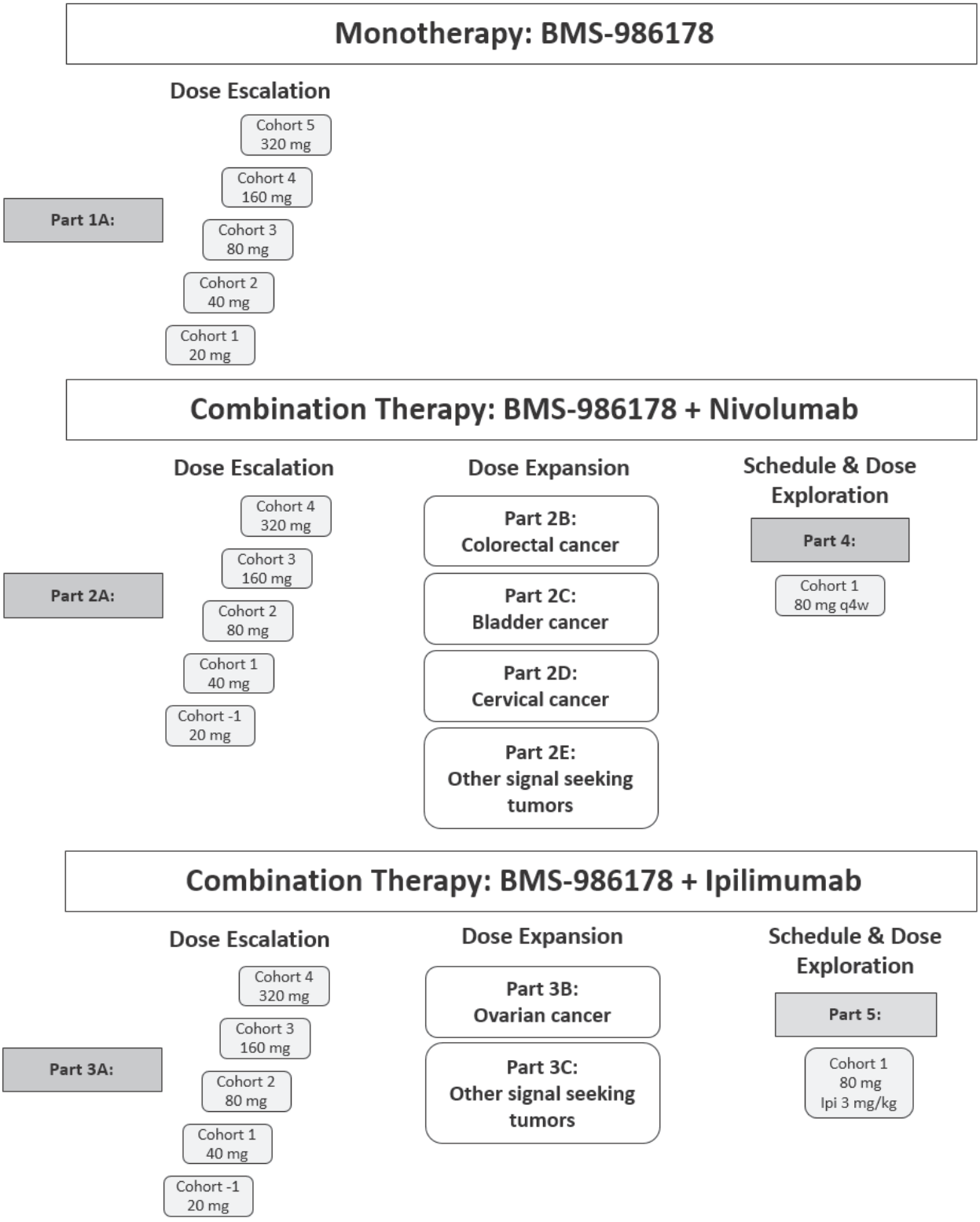
[redacted]

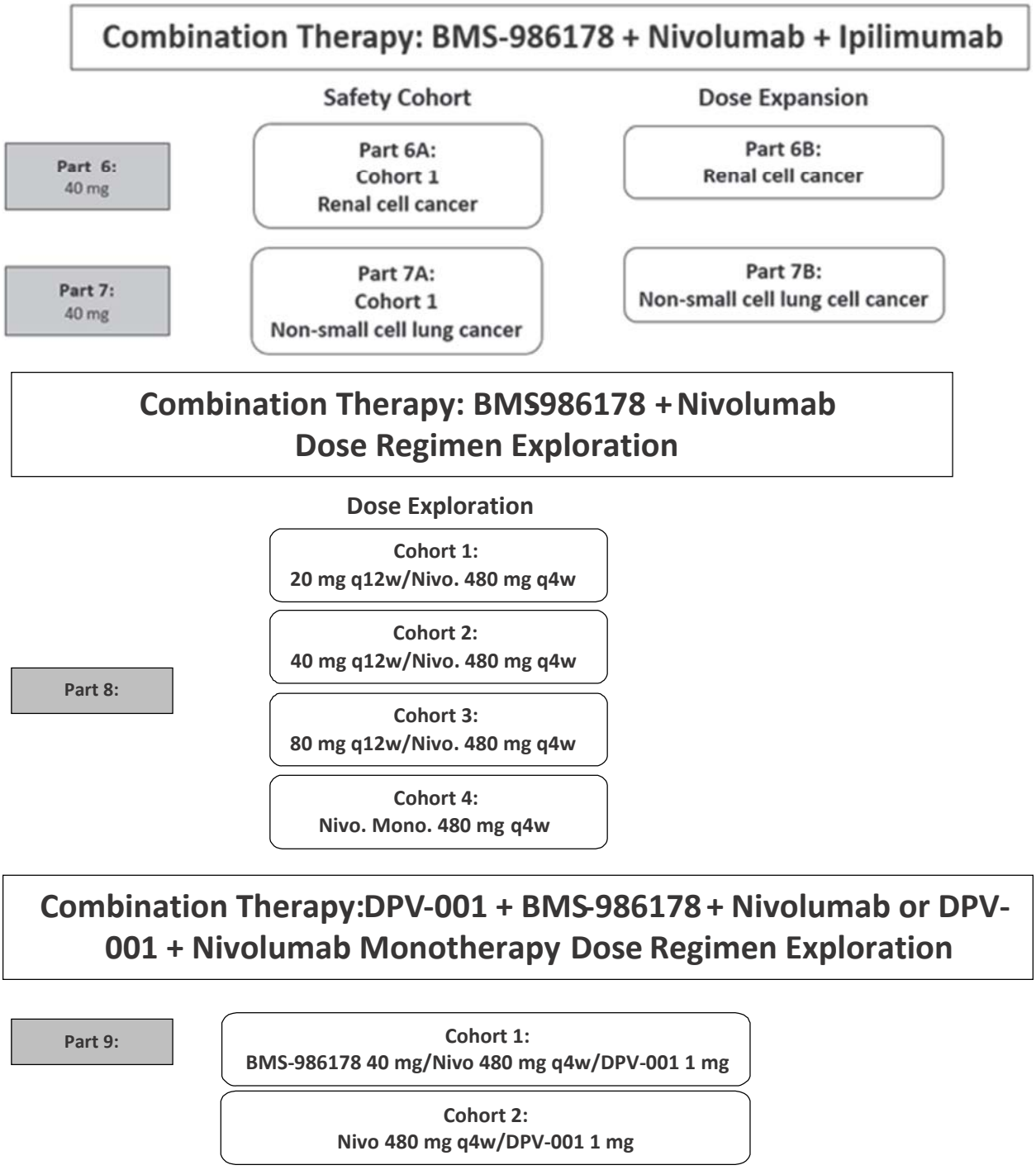
Study Design:

This is a Phase 1/2a, open-label study of BMS-986178 in subjects with advanced solid tumors that integrates initial BMS-986178 monotherapy with subsequent nivolumab and/or ipilimumab combination therapy or with nivolumab and DPV-001 combination therapy. Study sections (dose escalation and dose expansion) will proceed in a phased approach that is based upon study-emergent safety, PK, and PD data. The first section of the study will begin with BMS-986178 monotherapy dose escalation cohorts. The clinical data from the first 3 monotherapy dose cohorts will serve as a foundation for initiating dose escalation of BMS-986178 in combination with nivolumab. The clinical data from the first 3 monotherapy dose cohorts in addition to the clinical data from the first cohort of BMS-986178 in combination with nivolumab will then serve as a foundation for initiating dose escalation of BMS-986178 in combination with ipilimumab. The clinical data for BMS-986178 in combination with nivolumab and BMS-986178 in combination with ipilimumab will serve as the foundation for initiating combination therapy of BMS-986178 with nivolumab and ipilimumab in Parts 6 and 7. After establishment of a tolerable and pharmacologically active MTD/RP2D of BMS 986178 in the dose escalation and schedule and dose exploration sections, dose expansion in

specific tumor cohorts will be initiated. Recent preclinical and clinical data will serve as the foundation for focusing on further optimizing the dose of BMS-986178 in combination with nivolumab. As of Revised Protocol 5b, Parts 1-8 have been completed and Part 9 will be initiated.

Figure 1: Study Design Schematic (Parts 1 to 9)





Dose levels are specific for each part. Dose expansion will begin only after MTD/RP2D determination in the corresponding dose escalation phases of the study.

Abbreviations: MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose.

Summary of Study Design:

Dose Escalation (Parts 1A, 2A, and 3A):

The dose escalation part of the study will evaluate the safety and tolerability of BMS-986178 alone or in combination with nivolumab or ipilimumab in subjects with advanced solid tumors.

The initial dose level of BMS-986178 planned for this study is 20 mg. Dose escalation decisions for subsequent doses will be based on DLTs using a Bayesian Logistic Regression Method (BLRM; for BMS-986178 monotherapy) or a BLRM (-Copula) model (for BMS-986178 in combination with nivolumab and/or ipilimumab). The DLT period is 28 days for both monotherapy and combination therapy dose escalation parts. The DLT rate will be determined based on the incidence, severity, and duration of AEs that occur within the DLT period and for which no alternative cause can be identified. Dose selection for the next monotherapy cohort/dose level will take into account the BLRM (-Copula) recommendation in conjunction with the clinical recommendation and all available PK, PD, immunogenicity, and clinical and laboratory safety data from all treated subjects. Starting dose selection of BMS-986178 for Part 2A will be determined using data available from Part 1A, including clinical and laboratory safety assessments, PK/PD data, immunogenicity, and modeling recommendation within Bayesian modeling framework by incorporating single-agent toxicity profiles of both BMS-986178 (Part 1A) and nivolumab (CA209003). Starting dose selection of BMS-986178 for Part 3A will be determined using data available from Parts 1A and 2A, including clinical and laboratory safety assessments, PK/PD data, and modeling recommendation within Bayesian modeling framework by incorporating single-agent toxicity profiles of both BMS-986178 (Part 1A) and ipilimumab (CA184022). The final dose escalation decision will be made after discussion and agreement between the investigators and the BMS Medical Monitor. Actual doses can be modified per the BLRM (-Copula) but will not exceed doubling of the previously tested doses. Escalation by more than 1 dose level (dose skipping) is not permitted.

During dose escalation for all dose cohorts, the initial subject (sentinel subject) will be observed for 5 days before additional subjects in that cohort are treated with study drug.

Approximately 30 subjects will be enrolled in each dose escalation part. The number of subjects in each dose escalation cohort may vary depending on the BLRM (-Copula) recommendations. Initially, approximately 3 subjects will be treated at the starting dose levels of BMS-986178 or BMS-986178 in combination with nivolumab or ipilimumab. Additional cohorts of approximately 3 evaluable subjects will be treated at recommended dose levels per BLRM (-Copula) during the dose escalation phase. At least 6 DLT-evaluable subjects will be treated at the MTD.

Part 1A: Enrollment will begin in Part 1A, BMS-986178 monotherapy dose escalation. The initial dose of BMS-986178 for Part 1A will be 20 mg with expected subsequent doses of 40, 80, 160, and 320 mg. Actual doses can be modified per the BLRM but will not exceed doubling of the previously tested dose.

Parts 2A and 3A: Part 2A is the combination arm of BMS-986178 with nivolumab that will be initiated only after **at least** 3 dose levels in the monotherapy dose escalation have been found to be tolerated or an MTD/RP2D has been determined in the monotherapy dose escalation (Part 1A). The starting dose of BMS-986178 in Part 2A will be at least 1 dose level below a dose that was demonstrated to be tolerated in Part 1A, and at no time will the dose for BMS-986178 in Part 2A exceed the highest tolerated dose in Part 1A. To ensure further safety of the combination. Part 3A is the combination arm of BMS-986178 with ipilimumab that will be initiated only after at least 3 dose levels in the monotherapy dose escalation have been found to be tolerated or an MTD/RP2D has been determined in the monotherapy dose escalation (Part 1A) **and** at least 1 dose cohort has been found to be tolerated in the BMS-986178 with nivolumab dose escalation part (Part 2A). The starting dose of BMS-986178 in Part 3A will be at least 1 dose level below a dose that was demonstrated to be tolerated in Part 1A, and at no time will the dose for BMS-986178 in Part 3A exceed the highest tolerated dose in Part 1A to further ensure safety of the combination doses in treated subjects. In Parts 2A and 3A, doses intermediate to previously tested doses or doses lower than the starting dose may be explored to further characterize the dose response for safety, PK, or PD as appropriate based on clinical data collected.

Schedule and Dose Exploration (Parts 4, 5, 8, and 9):

Part 4: Part 4 is the combination arm of BMS-986178 with nivolumab (480 mg) to be administered every 4 weeks (q4w). The dose of BMS-986178 will be a dose previously evaluated in Part 2A that has been found to have a manageable safety profile and at no time will the dose for BMS-986178 exceed the highest tolerated dose in Part 2A, in which every 2 weeks (q2w) dosing is explored. Approximately 6 to 12 subjects will be treated in this cohort.

Part 5: Part 5 is the combination arm of BMS-986178 with ipilimumab (3 mg/kg) to be administered every 3 weeks (q3w) for 4 doses, followed by monotherapy with BMS-986178 (maintenance therapy). The dose of BMS-986178 will be a dose previously evaluated in Part 3A that has been found to have a manageable safety profile and at no time will the dose for BMS-986178 exceed the highest tolerated dose in Part 3A. Approximately 6 to 12 subjects will be treated in this cohort.

Part 8: Part 8 is the dose regimen exploration arm of BMS-986178 with a less frequent dosing schedule at either 20 mg, 40 mg, and 80 mg q12w in combination with nivolumab flat dose (480 mg; q4w) dose level (Cohort 1-3) or nivolumab 480 mg flat dose q4w monotherapy (Cohort 4) A tetanus vaccine (Tdap preferred, Td or equivalent after discussion with the medical monitor) will be administered to all subjects on Cycle 1 Day 1. Approximately 20 subjects will be treated in each cohort. Administration of a recall antigen such as tetanus toxoid may provide potent recall response with BMS-986178 in combination with nivolumab or nivolumab monotherapy.

Part 9: Subjects will be randomized to cohort 1 or cohort 2 in Part 9.

Part 9: Cohort 1

Is a combination of BMS-986178, nivolumab, DPV-001 vaccine, and single dose cyclophosphamide.

3 days prior to C1D1, a single-dose cyclophosphamide 300 mg/m^2 is to be administered IV over a 30 to 60 minute infusion.

On C1D1 the subjects will receive DPV-001 followed by BMS-986178. DPV-001 on C1D1 will consist of both UbiLT3 0.5 mg IN and UbiLT6 0.5 mg IN by ultrasound guidance (total of 1.0 mL suspension, 0.5 mL suspension UbiLT3 into 1 lymph node and 0.5 mL of UbiLT6 into another lymph node). After the DPV-001, the subject will be administered BMS-986178, as a flat dose of 40 mg over a 30 minute infusion.

On C1D8, the subject will receive only DPV-001. DPV-001 will consist of both UbiLT3 and UbiLT6, at the same dose listed on C1D1, but it will be administered ID.

On C1D15, the subject will receive DPV-001 followed by nivolumab. DPV-001 will consist of only UbiLT3 1 mg ID. After the administration of UbiLT3, the subject will be administered nivolumab at 240 mg infusion over 30 minutes.

Starting at cycle 2, nivolumab will be given on day 1 of each cycle as a 480 mg flat dose (q4w) infusion over 30 minutes. BMS-986178 40 mg infusion will only be given on day 1 of cycles 1-6, 9, and 12. DPV-001 1 mg ID will alternate between either UbiLT3 or UbiLT6. UbiLT6 will be given on C2D1, C3D1, C5D1, and C9D1. UbiLT3 1 mg ID will be given on C2D15, C4D1, C6D1, and C12D1.

Part 9: Cohort 2

Is a combination of nivolumab, DPV-001 vaccine, and single dose cyclophosphamide.

3 days prior to C1D1, a single-dose cyclophosphamide 300 mg/m^2 is to be administered IV over a 30 to 60 minute infusion.

On C1D1, the subjects will receive DPV-001. DPV-001 on C1D1 will consist of both UbiLT3 0.5 mg IN and UbiLT6 0.5 mg IN by ultrasound guidance (total of 1.0 mL suspension, 0.5 mL suspension UbiLT3 into 1 lymph node and 0.5 mL of UbiLT6 into another lymph node).

On C1D8, the subjects will receive only DPV-001. DPV-001 will consist of both UbiLT3 and UbiLT6 at the same dose listed on C1D1, but it will be administered ID.

On C1D15, the subjects will receive DPV-001 followed by nivolumab. DPV-001 will consist of only UbiLT3 1 mg ID. After the administration of UbiLT3, the subject will be administered nivolumab at 240 mg infusion over 30 minutes.

Starting at cycle 2, nivolumab will be given on day1 of each cycle as a 480 mg flat dose (q4w) infusion over 30 minutes. DPV-001 1 mg ID will alternate between either UbiLT3 or UbiLT6. UbiLT6 will be given on C2D1, C3D1, C5D1, and C9D1. UbiLT3 1 mg ID will be given on C2D15, C4D1, C6D1, and C12D1.

Safety Cohorts (Parts 6A ,7A):

Part 6A: Part 6A is the safety cohort for combination of BMS-986178 with ipilimumab and nivolumab in subjects with renal cell carcinoma (RCC). BMS-986178 will be administered at a flat dose of 40 mg in combination with

nivolumab (240 mg) and ipilimumab (1 mg/kg) q3w during Cycles 1 to 4 followed by maintenance therapy in which BMS-986178 (40 mg) and nivolumab (480 mg) will be administered q4w.

Part 7A: Part 7A is the safety cohort for combination of BMS-986178 with ipilimumab and nivolumab in subjects with non-small cell lung cancer (NSCLC). BMS-986178 will be administered at a flat dose of 40 mg (q2w) in combination with nivolumab (240 mg; q2w) and ipilimumab (1 mg/kg; q6w) for four 6-week cycles.

Dose Expansion (Parts 2B, 2C, 2D, 2E, 3B, 3C, 6B, and 7B):

Treatment in the dose expansion cohorts will be initiated when the MTD/RP2D has been determined based on the evaluation of totality of available clinical safety (DLTs, AEs occurring after the DLT period), PK, PD, immunogenicity, and modeling data from the dose escalation parts (1A, 2A, and 3A) or schedule and dose exploration parts (4 and 5). Approximately 294 subjects will be treated in all dose expansion cohorts.

Parts 2B, 2C, 2D, and 2E (combination with nivolumab) are the dose expansion parts in subjects with colorectal cancer, bladder cancer, cervical cancer, and other tumors from dose escalation for signal finding, respectively, at the MTD/RP2D(s) determined in Parts 2A or 4.

Part 3B (combination with ipilimumab) is the dose expansion part in subjects with ovarian cancer at the MTD/RP2D(s) determined in Parts 3A or 5. Part 3C (combination with ipilimumab) is the dose expansion part in subjects with other tumors from dose escalation for signal finding at the MTD/RP2D(s) determined in Part 3A or 5.

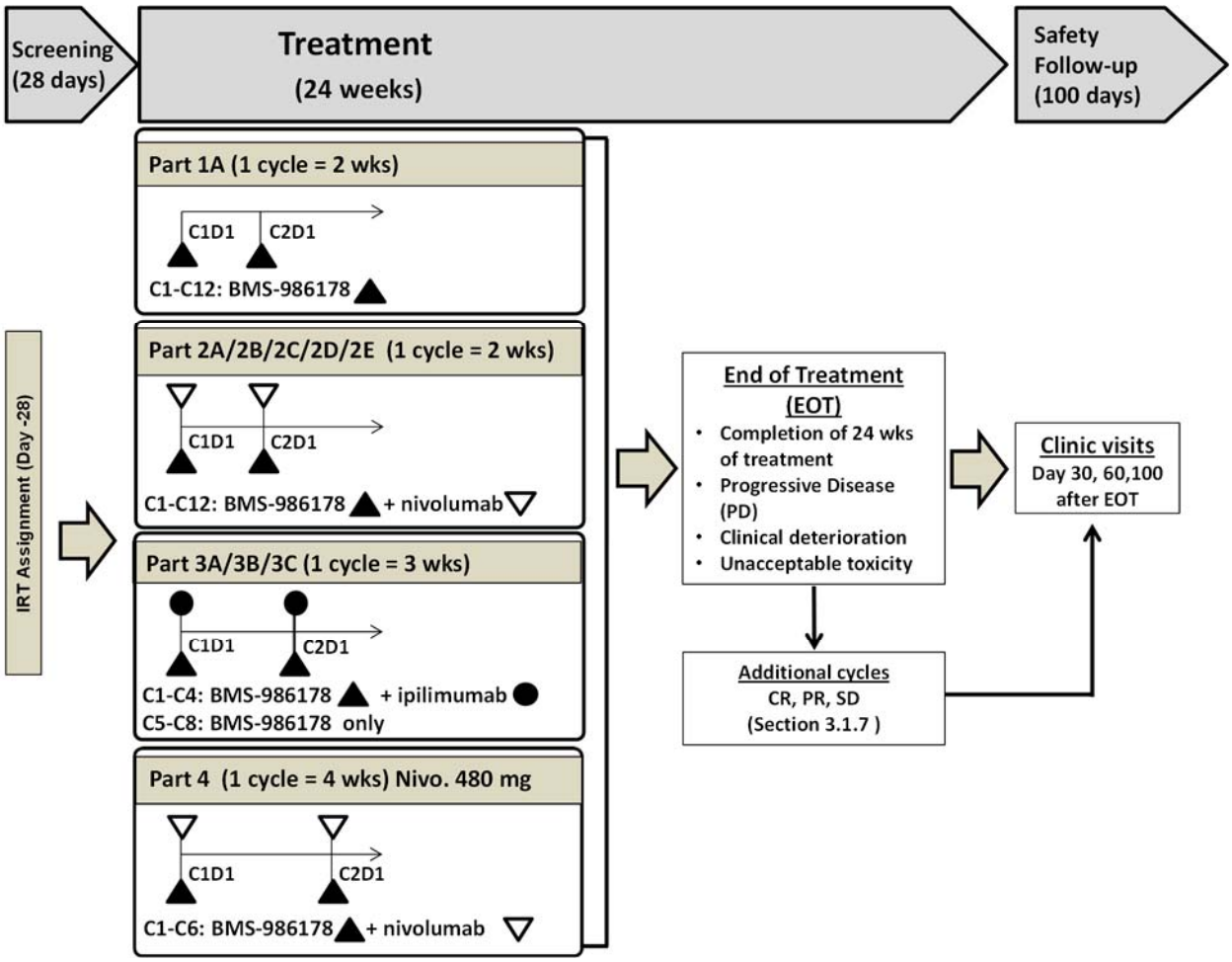
Part 6B (combination with nivolumab and ipilimumab) is the dose expansion part in subjects with RCC at a tolerable dose determined in Part 6A.

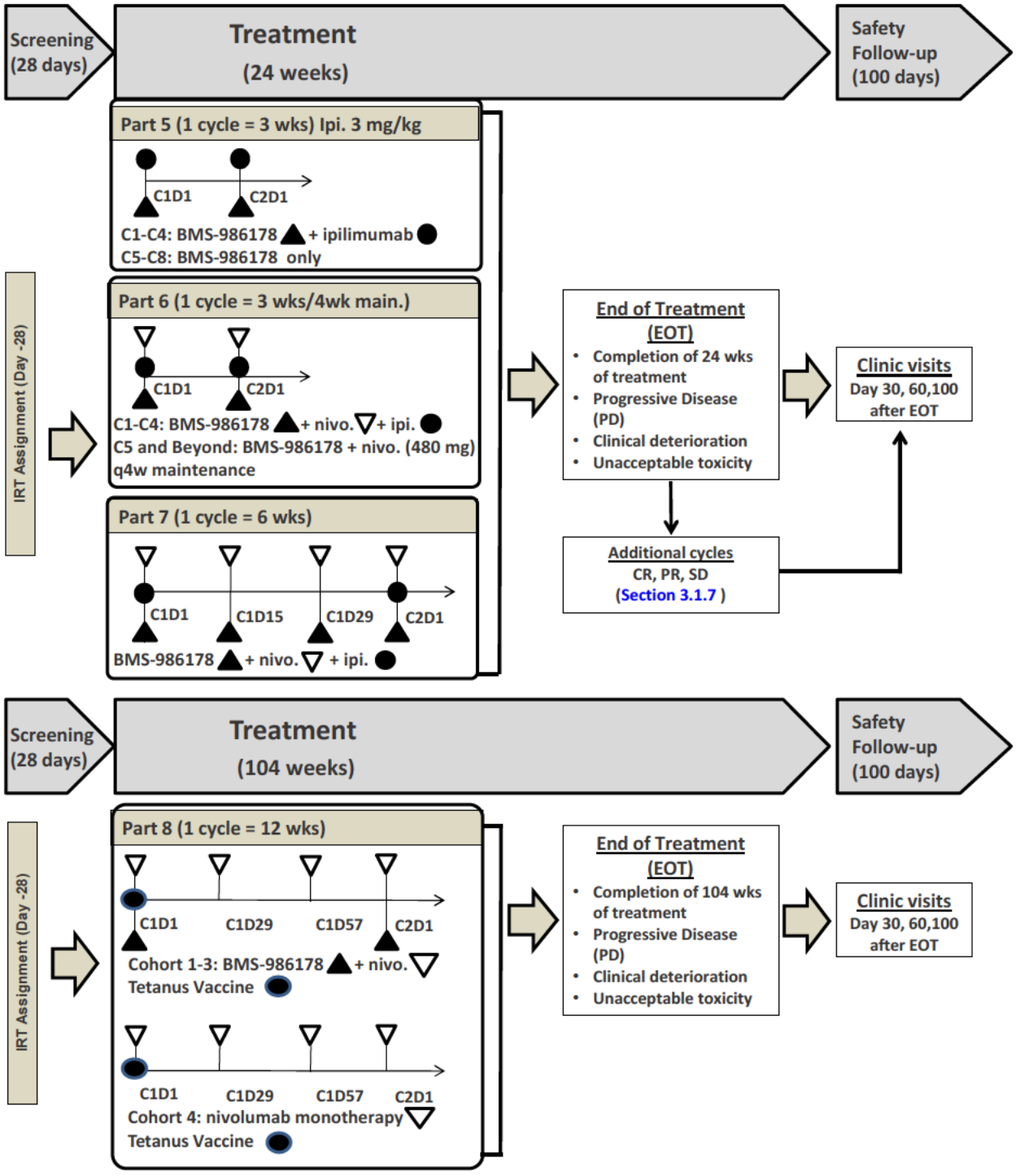
Part 7B (combination with nivolumab and ipilimumab) is the dose expansion part in subjects with NSCLC at a tolerable dose determined in Part 7A.

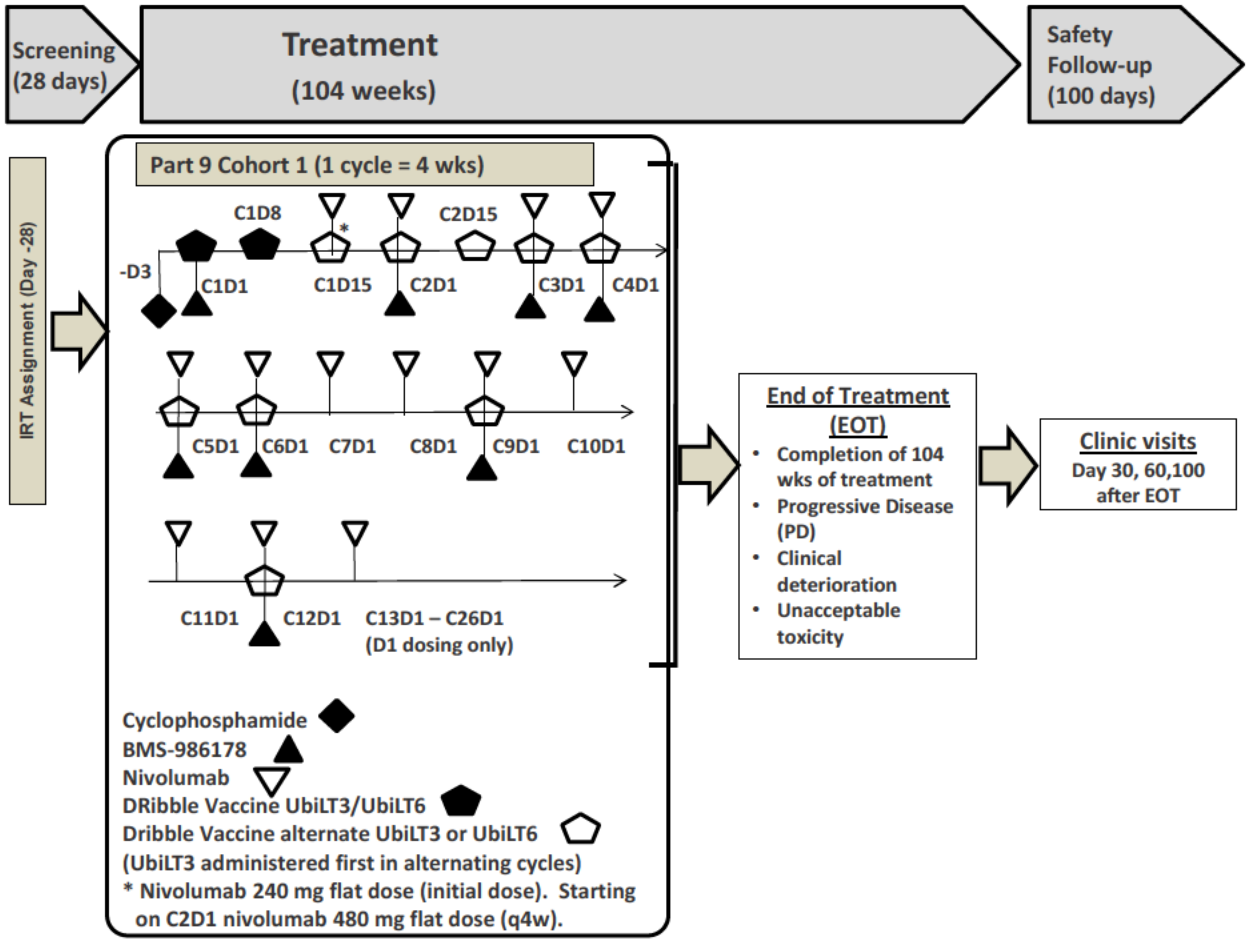
Summary of Study Periods:

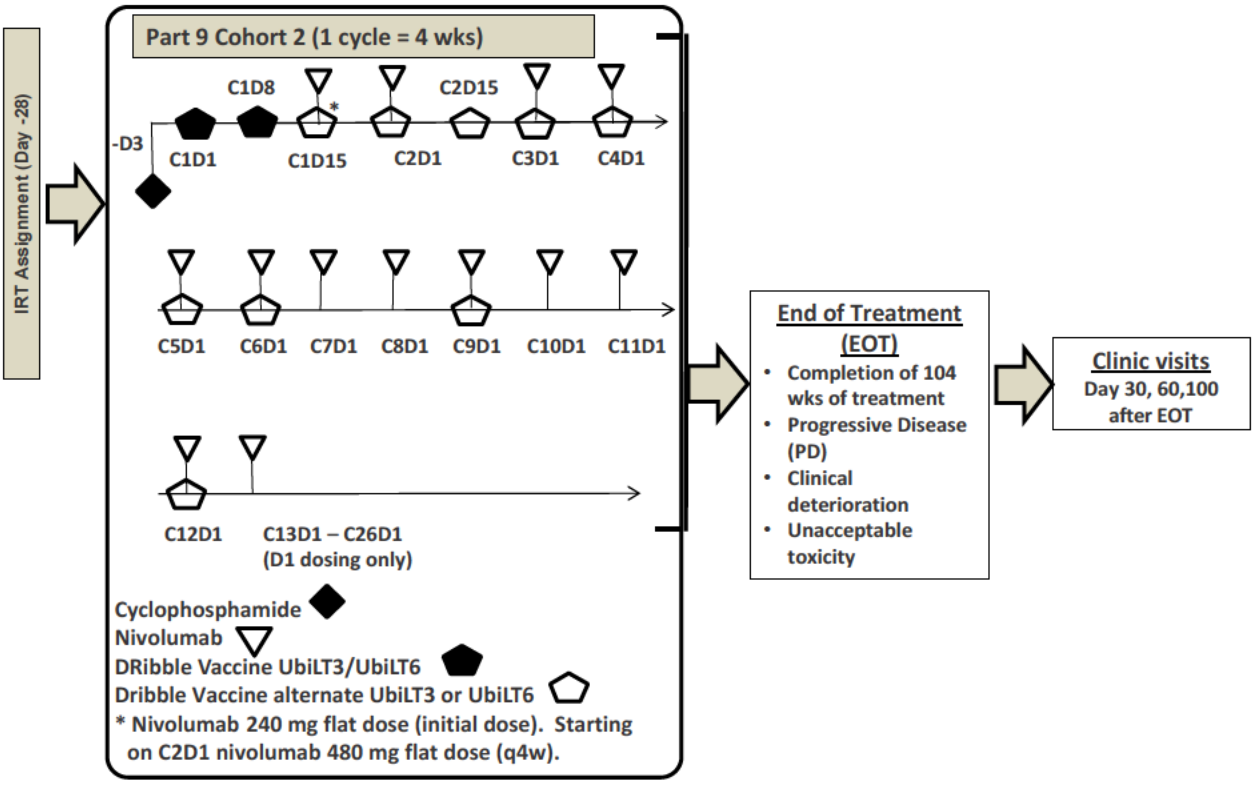
Subjects will complete: Screening (up to 28 days), Treatment (up to 24 weeks of dosing for Part 1-7, up to 24 months of dosing for Parts 8 and 9, or until meeting protocol-specified discontinuation criteria) and Safety Follow-up of approximately 100 days. As of Protocol Revision 05b, no new subjects will enter the Response Follow-up or Survival Follow-up. Any subjects in Part 2, 4, 6, or 7 may be eligible for an additional 18 months of study therapy beyond the initial 24 weeks. Part 8 and Part 9 subjects will not be eligible for treatment with additional cycles. The maximum treatment allowed for any subject is 2 years from the first dose of study treatment regardless of dose delays. The study visit schematic is presented in Figure 2.

Figure 2: Study Visit Schematic









Abbreviations: CR = complete response; EOT = end of treatment; Ipi = ipilimumab; IRT = Interactive Response Technology; Nivo = nivolumab; PR = partial response; SD = stable disease; wks = weeks.

Screening Period:

The Screening period will last for up to 28 days. The screening period begins by establishing the subject's initial eligibility and signing of the informed consent form. Subjects will be enrolled using an Interactive Response Technology (IRT).

Treatment Period:

The Treatment period consists of up to 24 weeks of dosing for Parts 1-7. Parts 8 and 9 will each have a treatment period for up to 24 months of dosing. Following each treatment cycle, the decision to treat a subject with the next cycle of study therapy, up to 24 weeks of treatment for Parts 1-7 or up to 24 months for Parts 8 and 9, will be based on risk/benefit and tumor assessments. Tumor assessments will be performed every 8 weeks for Parts 1-7 and 9 or every 12 weeks for Part 8 (± 1 week). Assessments of partial response (PR) and complete response (CR) must be confirmed at least 4 weeks following initial assessment. Tumor progression or response endpoints will be assessed using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1.

Subjects with a response of stable disease (SD), PR, or CR at the end of a given cycle will continue to the next treatment cycle. Subjects will generally be allowed to continue study therapy until the first occurrence of one of the following: 1) completion of the maximum number of cycles; 2) progressive disease; 3) clinical deterioration suggesting that no further benefit from treatment is likely; 4) intolerability to therapy; or 5) meeting the criteria for discontinuation of study therapy as outlined in the protocol.

Safety Follow-up:

Upon completion of study therapy, subjects will enter the Safety Follow-up period. After the end of treatment (EOT) visit, subjects will be evaluated for any new adverse events (AEs) for approximately 100 days after the last dose of therapy. Follow-up visits should occur at Days 30, 60 and 100 after the last dose or the date of discontinuation.

Subjects (except those who withdraw consent for study participation) are expected to complete the 3 clinical Safety Follow-up visits regardless of whether they start new anti-cancer therapy.

Duration of Study: The total duration of study time for any individual subject is expected to be approximately 2.5 years (depending on Part subject is randomized to). The study will end when the last subject completes their last study visit, which is planned to be about 4 years after the start of the study.

Number of Subjects: Approximately 632 subjects will be enrolled, and approximately 539 subjects will be treated in the study.

Study Population: Subjects must be at least 18 years old and have histologic or cytologic confirmation of a malignancy that is advanced (metastatic, recurrent, refractory and/or unresectable) with measurable disease per RECIST v1.1.

Study Drug: Investigational products are as listed in Table -1.

Table -1: Study Drugs for CA012004

Product Description Class and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Packaging/	Product Description Class and Dosage Form
BMS-986178 Injection	25 mg/mL (80 mg/vial)	IP	Open Label	Vial	Store at 2°C to 8°C; do not freeze; protected from light.
Nivolumab Injection	10 mg/mL (100 mg/vial)	IP	Open Label	Vial	Store at 2°C to 8°C; store in original package; do not freeze; protected from light.
Ipilimumab Injection	5 mg/mL (200 mg/vial)	IP	Open Label	Vial	Store at 2°C to 8°C; do not freeze; protected from light.
Tetanus vaccine	Per local[a]	IP	Open Label	Various packaging configurations	Refer to the label on container and/or package insert
UbiLT3 and UbiLT6 vaccine[b]	1 mg/mL and as per Pharmacy Manual	IP	Open Label	Vial and various packaging configurations	Refer to label on container and/or package insert or pharmacy manual

Abbreviation: IB = Investigator Brochure; IP = investigational product

[a] Tetanus vaccine (Tdap preferred, Td or equivalent after discussion with the medical monitor)will be obtained as local commercial product in countries if allowed by local regulations or through investigating sites standard prescribing procedures.

[b] DPV-001(UbiLT3 and UbiLT6) will be provided by Ubivac

Study Assessments:

- Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Subjects will be closely monitored for AEs throughout the study.
- Safety Assessments: AEs will be assessed during the study and for 100 days after the last treatment. AEs will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities and reviewed for potential significance and importance. Subjects will be followed until all treatment-related AEs have recovered to baseline or are deemed irreversible by the investigator.
- Efficacy Assessments: Disease assessment with computed tomography and/or magnetic resonance imaging as appropriate will be performed at baseline and every 8 weeks (± 1 week) per RECIST v1.1 until discontinuation of treatment or withdrawal from study. Tumor assessments at other time points may be performed if the investigator is concerned about tumor progression. Assessment of tumor response will be reported by the investigator as defined by RECIST v1.1 for subjects with advanced solid tumors.
- Pharmacokinetic and Immunogenicity Assessments: Samples for PK and immunogenicity assessments will be collected for subjects receiving BMS-986178 alone, in combination with nivolumab and/or ipilimumab, or in combination with nivolumanb and DPV-001. The PK of BMS-986178 will be characterized by non-compartmental analysis method. Immunogenicity samples will be analyzed for anti-BMS-986178 antibodies and/or anti-nivolumab antibodies and/or anti-ipilimumab antibodies by validated immunoassays.

[redacted]

Statistical Considerations:

Sample Size Determination:

Dose Escalation (Parts 1A, 2A, and 3A):

As a Phase 1 dose escalation trial, the sample size for each dose escalation cohort depends on observed toxicity and posterior inference. Approximately 30 subjects are expected to be treated during each dose escalation part (BMS-986178 monotherapy [Part 1A], BMS-986178 in combination with nivolumab [Part 2A], and BMS-986178 in combination with ipilimumab [Part 3A]) for a combined total of approximately 90 subjects in Parts 1A, 2A and 3A. Initially, approximately 3 subjects will be treated at the starting dose levels of BMS-986178 or BMS-986178 in combination with nivolumab or ipilimumab. Additional cohorts of approximately 3 evaluable subjects will be treated at recommended dose levels per BLRM (-Copula) recommendations during the dose escalation phase. At least 6 DLT-evaluable subjects will be treated at the MTD.

Schedule and Dose Exploration (Parts 4, 5, 8, and 9):

Approximately 6 to 12 subjects are expected to be treated during each schedule and dose exploration part (BMS-986178 in combination with nivolumab [Part 4] and BMS-986178 in combination with ipilimumab [Part 5] for a combined total of approximately 12 to 24 subjects in Parts 4 and 5).

Approximately 20 evaluable subjects per dose cohort will be treated in Part 8 of the study, BMS-986178 in combination with nivolumab (Cohort 1-3) and monotherapy nivolumab (Cohort 4). Total number of subjects in this Part 8 will be approximately 80.

In Part 9, subjects will be treated with DPV-001 vaccine, single dose cyclophosphamide and nivolumab with/without BMS 986178. There will be a total of approximately 18 subjects combined in Cohorts 1 and 2 of Part 9, with a possibility of 20% over enrollment. Part 9 may be further expanded to 24 subjects for Cohort 1 and 12 subjects for Cohort 2.

Safety Cohorts (Parts 6A and 7A):

Approximately 6 to 12 subjects are expected to be treated during each safety cohort part (BMS-986178 in combination with nivolumab and ipilimumab q3w, followed by maintenance therapy with combination of BMS-986178 and nivolumab q4w [Part 6A], BMS-986178 in combination with nivolumab [q2w] and ipilimumab [q6w; Part 7A]), for a combined total of approximately 12 to 24 subjects in Parts 6A and 7A.

Cohort Expansion (Parts 2B, 2C, 2D, 2E, 3B, 3C, 6B, and 7B):

In general terms, the expansion phase sizing is guided by Simon 2-stage design, which is based on target response rates (target overall response rate) and the ability to identify a signal for such clinical response that is above the standard of care (historical overall response rate). It is not the intent of this study to use Simon 2-stage design for formal hypothesis testing.

Disease-restricted population cohorts will be guided by the Simon 2-stage design. Approximately 35 subjects will be treated in the Part 2B dose expansion cohort. Approximately 27 subjects will be treated in the Part 2C dose expansion cohort. Approximately 37 subjects will be treated in the Part 2D dose expansion cohort. Approximately 35 subjects will be treated in the Part 3B dose expansion cohort. Approximately 40 subjects will be treated in each Parts 2E and 3C of dose expansion portion will include other tumors from dose escalation for signal seeking. Due to the heterogeneity of response rates of the mixed tumors, Simon 2-stage design is not pursued for Parts 2E and 3C. Approximately 40 subjects each will be treated in dose expansion Parts 6B and 7B. Additional subjects may be treated in order to have sufficient response-evaluable subjects per expansion cohort.

Endpoints:

Primary Endpoints:

The assessment of safety will be based on the incidence of AEs, serious AEs, AEs leading to discontinuation, and deaths. In addition, clinical laboratory test abnormalities will be examined.

Secondary Endpoints:

Efficacy: The anti-tumor activity of BMS-986178 alone, in combination with nivolumab and/or ipilimumab, or in combination with nivolumab and DPV-001 and nivolumab in combination with DPV-001 will be measured by ORR based on RECIST v1.1. The above will be determined based on tumor measurements occurring at baseline, every 8 weeks (± 1 week) during the treatment period.

- Best overall response (BOR) is assessed by investigator and/or BICR per RECIST 1.1 criteria.
- ORR is defined as the proportion of all treated subjects whose BOR is either CR or PR.

Pharmacokinetics: Selected BMS-986178 parameters, such as Cmax, Tmax, AUC(0-t), and AUC(TAU), will be assessed in 2 cycles depending on the schedule for monotherapy or in combination with nivolumab and/or ipilimumab. Parameters such as Ctau, CLT, Css-avg, accumulation index (AI), and effective elimination half-life (T-HALFeff) will be assessed in the second cycle when intensive PK are collected. A separate listing, summary, and plot will be generated for Ctrough.

Immunogenicity: The secondary objective of immunogenicity will be assessed by the frequency of positive ADA to BMS-986178 or nivolumab or ipilimumab.

Pharmacodynamics: The secondary objective of pharmacodynamics will be assessed by the proportion of subjects showing a change in pharmacodynamic biomarkers such as soluble OX40 and peripheral OX40 receptor occupancy along with tumor pharmacodynamic of BMS-986178 in combination with nivolumab or nivolumab monotherapy (Part 8).

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Analyses:

Safety analyses: All recorded AEs will be listed and tabulated by system organ class, preferred term, and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator, and abnormalities, if present, will be listed.

Efficacy analyses: The efficacy analyses will be performed on all treated subjects. Efficacy analyses based on response-evaluable subjects may be performed for interim analyses when the minimum follow up period is less than sufficient to warrant adequate interpretation of results. Listing of tumor measurements will be provided by subject and study day in each arm and dose level. Individual subject's BOR will be listed based on RECIST 1.1.

To describe the anti-tumor activity of BMS-986178 alone, in combination with nivolumab and/or ipilimumab, or in combination with nivolumab and DPV-001 and nivolumab in combination with DPV-001, ORR will be calculated. ORR and corresponding 2-sided 95% CI by the Clopper-Pearson method will be provided by treatment and/or dose level and tumor type.

Pharmacokinetic analyses: All individual PK parameters will be listed for each analyte, including any exclusions and reasons for exclusion from summaries. Summary statistics will be tabulated for each PK parameter by treatment. Geometric means and coefficients of variation will be presented for Cmax, AUC(0-t), AUC(TAU), Ctau, CLT, Css-avg, and AI. Medians and ranges will be presented for Tmax. Means and standard deviations will be presented for all other PK parameters (eg, T-HALFeff).

BMS-986178 dose dependency will be assessed in dose escalation monotherapy. To describe the dependency on dose of BMS-986178, scatter plots of Cmax, AUC(0-t), and AUC(TAU) versus dose may be provided for each day measured. An exploratory assessment of dose proportionality based on a power model and a CI around the power coefficient may be performed. Nivolumab and ipilimumab end of infusion and trough (Ctrough) concentrations and BMS-986178 trough concentration will be tabulated by treatment and study day using summary statistics. These data may also be pooled with other datasets for population PK analysis, which will be presented in a separate report.

Immunogenicity analysis: A listing of all available immunogenicity data will be provided by treatment, dose, and immunogenicity status. The frequency of subjects with positive ADA assessment of BMS-986178, nivolumab, and ipilimumab will be summarized.

Biomarker analyses: In Part 9, summary statistics for the proportion of subjects showing a change in pharmacodynamic biomarkers will be tabulated by treatment cohort.

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1.2 Research Hypothesis

It is anticipated that anti-OX40 agonist antibody (BMS-986178), administered as a single agent or in combination with anti-PD-1 antibody (nivolumab) or anti-CTLA-4 (ipilimumab) or DPV-001, will demonstrate adequate safety and tolerability, as well as a favorable risk/benefit profile, to support further clinical testing. No prospective hypotheses are being formally evaluated.

1.3 Objectives(s))

1.3.1 Primary Objective

The primary objective is to determine the safety, tolerability, DLTs, and MTD/RP2D of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab or DPV-001 in subjects with advanced solid tumors.

1.3.2 Secondary Objectives

Secondary Objectives for Parts 1-8

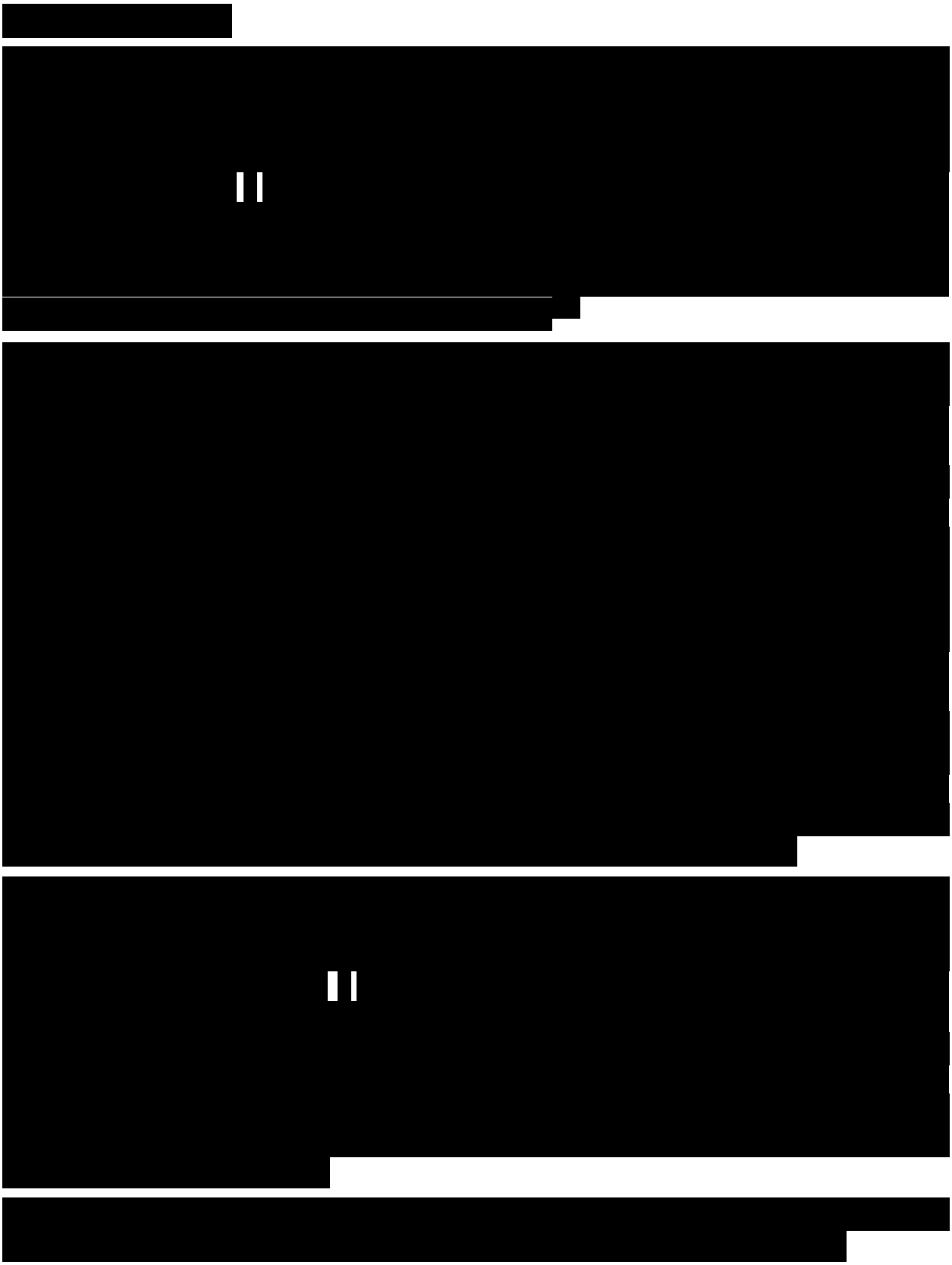
- To investigate the preliminary anti-tumor activity of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab, in subjects with advanced solid tumors
- To characterize the PK of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab
- To characterize the immunogenicity of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab, and the immunogenicity of nivolumab or ipilimumab administered with BMS-986178
- To assess the proportion of subjects showing a change in peripheral pharmacodynamic biomarkers such as soluble OX40 and peripheral OX40 receptor occupancy along with tumor pharmacodynamic of BMS-986178 in combination with nivolumab or nivolumab monotherapy (Part 8).

Secondary Objectives for Part 9

- To investigate the preliminary anti-tumor activity of BMS 986178 in combination with nivolumab and DPV-001 and nivolumab in combination with DPV-001 in subjects with TNBC and ER-low positive breast cancer.
- To characterize the pharmacokinetics (PK) of BMS 986178 in combination with nivolumab and DPV-001

- To characterize the immunogenicity of BMS 986178 in combination with nivolumab and DPV-001
- To assess the proportion of subjects showing a change in peripheral or tumor pharmacodynamic biomarkers such as sustained T cell expansion with DPV-001 in combination with nivolumab with or without BMS-986178

[redacted]



[redacted]

[redacted]

The overall safety profile of ipilimumab is well characterized and consists mainly of [redacted]

[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the ICH and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials

(eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the IB or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form(s) which will include all elements required by ICH, GCP, and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form(s) and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
- If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form(s) must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

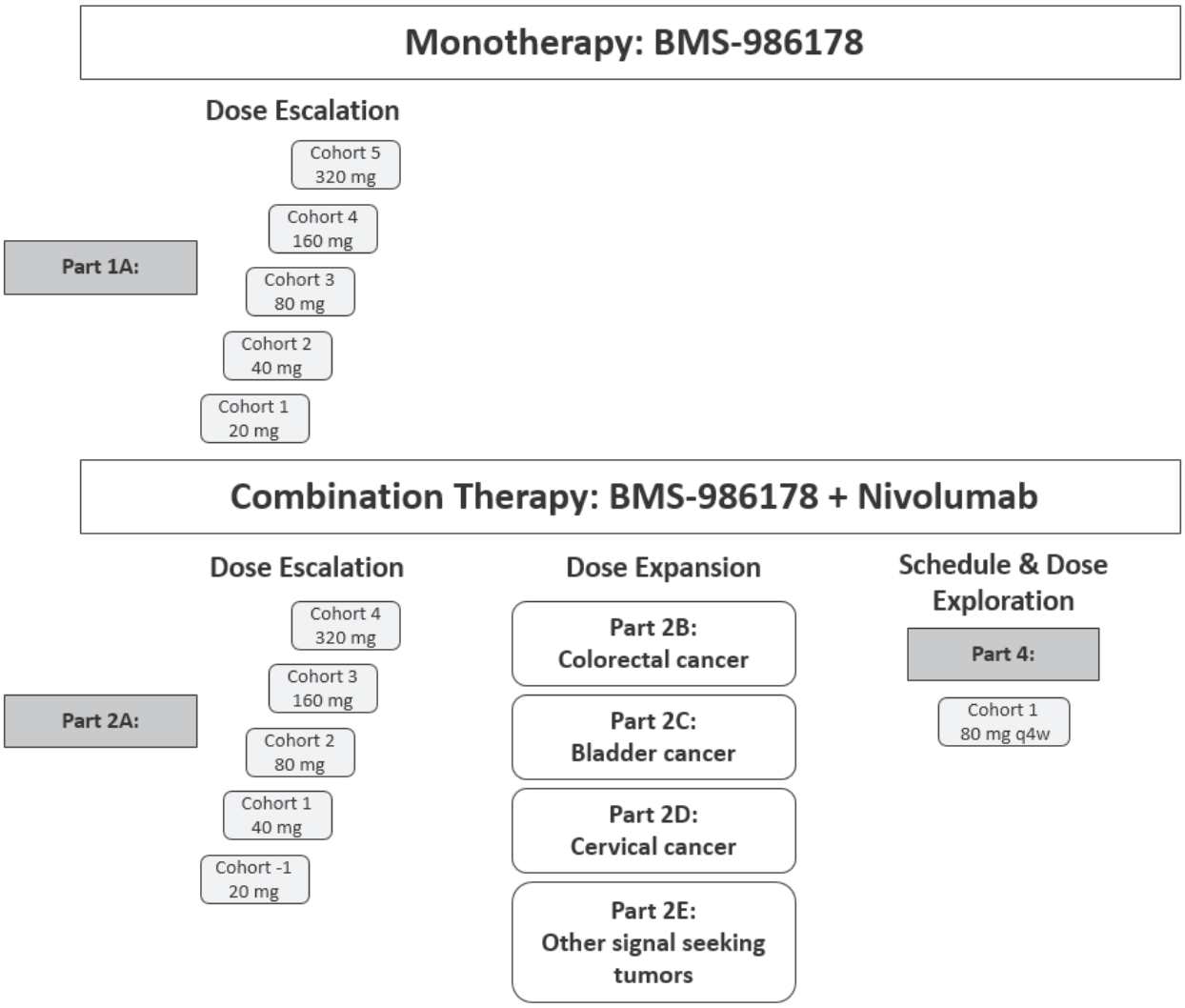
The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

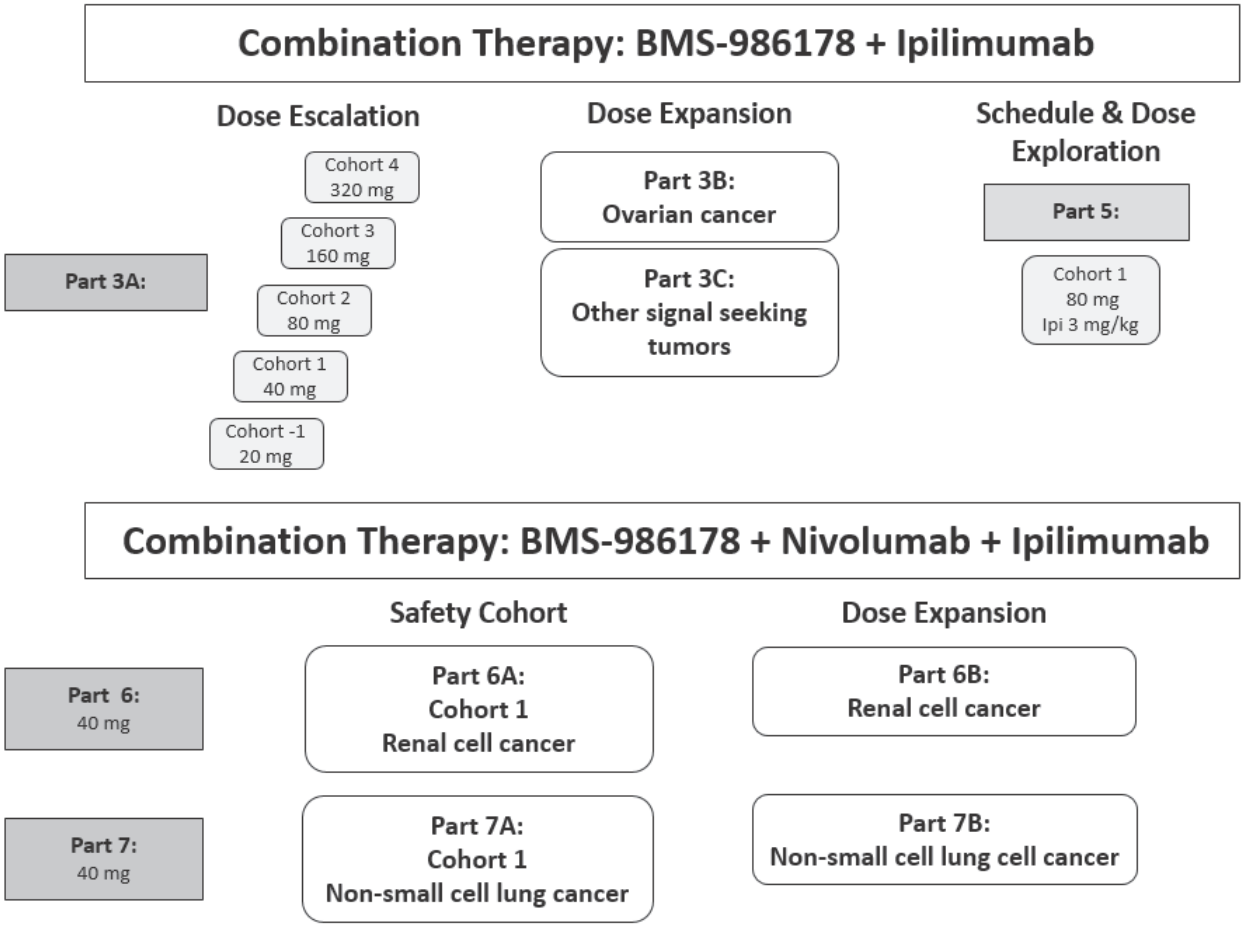
3 INVESTIGATIONAL PLAN

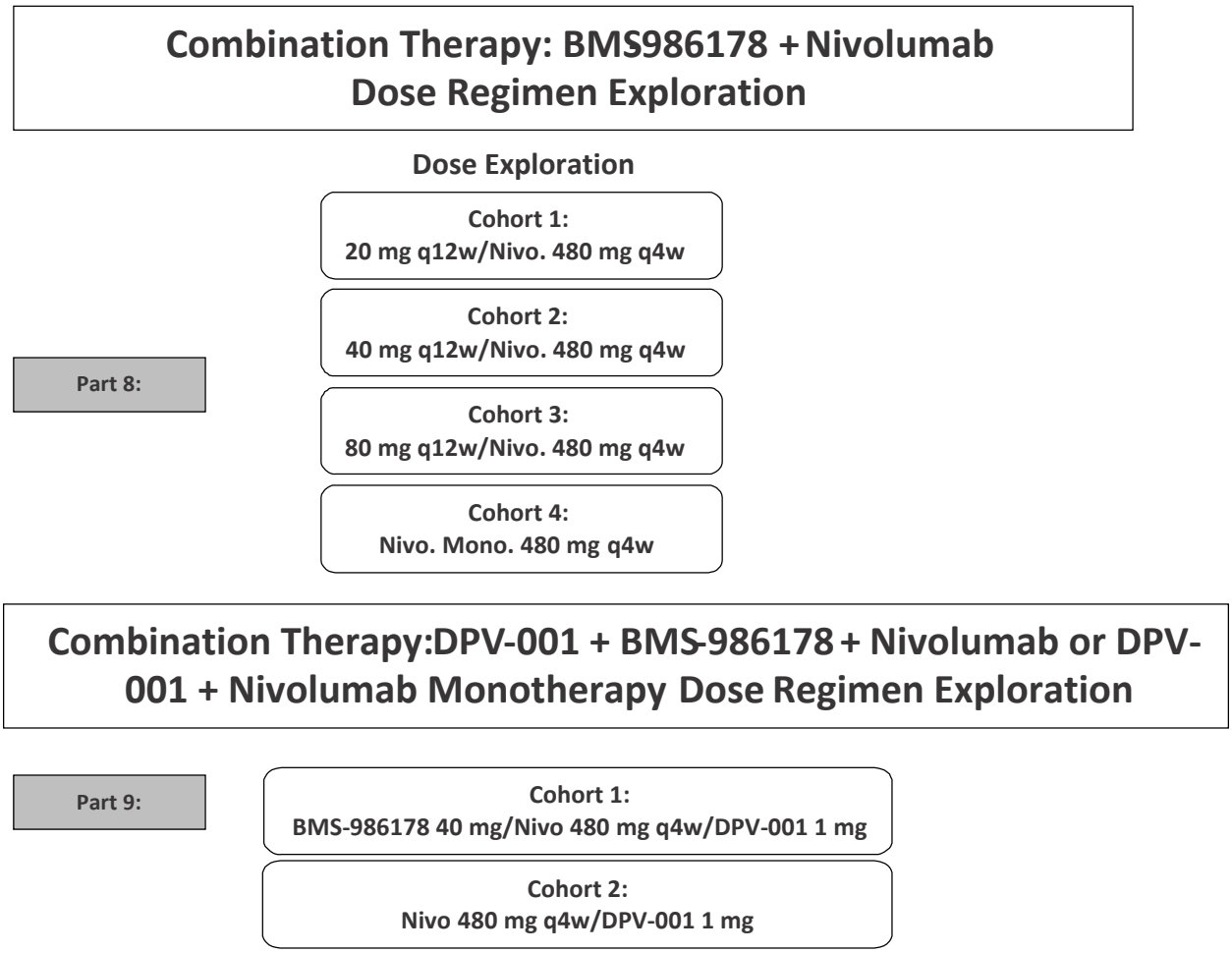
3.1 Study Design and Duration

This is a Phase 1/2a, open-label study of BMS-986178 in subjects with advanced solid tumors that integrates initial BMS-986178 monotherapy with subsequent nivolumab and/or ipilimumab or nivolumab and DPV-001 combination therapy (see Figure 3.1-1). Study sections (dose escalation and dose expansion) will proceed in a phased approach that is based upon study-emergent safety, PK, and PD data. The first section of the study will begin with BMS-986178 monotherapy dose escalation cohorts. The clinical data from the first 3 monotherapy dose cohorts will serve as a foundation for initiating dose escalation of BMS-986178 in combination with nivolumab. The clinical data from the first 3 monotherapy dose cohorts in addition to the clinical data from the first cohort of BMS-986178 in combination with nivolumab will then serve as a foundation for initiating dose escalation of BMS-986178 in combination with ipilimumab. The clinical data for BMS-986178 in combination with nivolumab and BMS-986178 in combination with ipilimumab will serve as the foundation for initiating combination therapy of BMS-986178 with nivolumab and ipilimumab in Parts 6 and 7. After establishment of a tolerable and pharmacologically active MTD/RP2D of BMS-986178 in the dose escalation and schedule and dose exploration sections, dose expansion in specific tumor cohorts will be initiated. Recent preclinical and clinical data will serve as the foundation for focusing on further optimizing the dose of BMS-986178 in combination with nivolumab.

Figure 3.1-1: Study Design Schematic (Parts 1 to 9)







Dose levels are specific for each part. Dose expansion will begin only after MTD/RP2D determination in the corresponding dose escalation phases of the study.
Abbreviations: MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose.

3.1.1 Study Outline (All Parts)

3.1.2 Dose Escalation (Parts 1A, 2A, and 3A)

The dose escalation part of the study will evaluate the safety and tolerability of BMS-986178 alone or in combination with nivolumab or ipilimumab in subjects with advanced solid tumors (listed in Section 3.3.1 [Inclusion criteria 2]).

The initial dose level of BMS-986178 planned for this study is 20 mg. Dose escalation decisions for subsequent doses will be based on DLTs using a BLRM (for BMS-986178 monotherapy) or a BLRM (-Copula) model (for BMS-986178 in combination with nivolumab or ipilimumab). The DLT period is 28 days for both monotherapy and combination therapy dose escalation parts. The DLT rate will be determined based on the incidence, severity, and duration of AEs that occur within the DLT period and for which no alternative cause can be identified. Dose selection for the next monotherapy cohort/dose level will take into account the BLRM (-Copula) recommendation (Section 3.1.2.4) in conjunction with clinical recommendation and all available PK, PD,

immunogenicity, and clinical and laboratory safety data from all treated subjects. Starting dose selection of BMS-986178 for Part 2A will be determined using data available from Part 1A, including clinical and laboratory safety assessments, PK/PD data, immunogenicity, and modeling recommendation within Bayesian modeling framework by incorporating single-agent toxicity profiles of both BMS-986178 (Part 1A) and nivolumab (CA209003). Starting dose selection of BMS-986178 for Part 3A will be determined using data available from Parts 1A and 2A, including clinical and laboratory safety assessments, PK/PD data, and modeling recommendation within Bayesian modeling framework by incorporating single-agent toxicity profiles of both BMS-986178 (Part 1A) and ipilimumab (CA184022). The final dose escalation decision will be made after discussion and agreement between the investigators and the BMS Medical Monitor. Actual doses can be modified per the BLRM (-Copula) but will not exceed doubling of the previously tested dose. In Parts 2A and 3A, doses intermediate to previously tested doses or doses lower than the starting dose may be explored to further characterize the dose response for safety, PK, or PD as appropriate based on clinical data collected.

During dose escalation for all dose cohorts, the initial subject (sentinel subject) will be observed for 5 days before additional subjects in that cohort are treated with study drug.

All safety signals throughout the conduct of the study will be reviewed by the BMS-986178 Medical Surveillance Team (MST). If unexpected safety findings are identified between scheduled MST meetings, an ad hoc meeting will be convened, as appropriate.

Approximately 30 subjects will be enrolled in each dose escalation part. The number of subjects in each dose escalation cohort may vary depending on the BLRM (-Copula) recommendations. Initially, approximately 3 subjects will be treated at the starting dose levels of BMS-986178 or BMS-986178 in combination with nivolumab or ipilimumab. Additional cohorts of approximately 3 evaluable subjects will be treated at recommended dose levels per BLRM (-Copula) during the dose escalation phase. At least 6 DLT-evaluable subjects will be treated at the MTD.

3.1.2.1 Part 1A: Monotherapy Dose Escalation

Part 1A is BMS-986178 monotherapy dose escalation. The initial dose of BMS-986178 for Part 1A will be 20 mg with expected subsequent doses of 40, 80, 160, and 320 mg. Dosing of BMS-986178 will begin on Day 1 of each cycle and will be administered q2w for up to 12 cycles.

3.1.2.2 Part 2A: Combination with Nivolumab Dose Escalation

Part 2A is the combination arm of BMS-986178 with nivolumab that will be initiated only after at least 3 dose levels in the monotherapy dose escalation have been found to be tolerated or an MTD/RP2D has been determined in the monotherapy dose escalation (Part 1A). The starting dose of BMS-986178 in Part 2A will be at least 1 dose level below a dose that was demonstrated to be tolerated in Part 1A to ensure further safety of the combination. At no time will the dose for BMS-986178 in Part 2A exceed the highest tolerated dose in Part 1A. Nivolumab will be administered at a flat dose of 240 mg. Each treatment cycle will be 2 weeks in length and study drugs will be administered q2w starting on Day 1 of each cycle for up to 12 cycles.

3.1.2.3 Part 3A: Combination with Ipilimumab Dose Escalation

Part 3A is the combination arm of BMS-986178 with ipilimumab that will be initiated only after **at least** 3 dose levels in the monotherapy dose escalation have been found to be tolerated or an MTD/RP2D has been determined in the monotherapy dose escalation (Part 1A) **and** at least 1 dose cohort has been found to be tolerated in the BMS-986178 with nivolumab dose escalation part (Part 2A). The starting dose of BMS-986178 in Part 3A will be at least 1 dose level below a dose that was demonstrated to be tolerated in Part 1A. At no time will the dose for BMS-986178 in Part 3A exceed the highest tolerated dose in Part 1A to further ensure safety of the combination doses in treated subjects. Ipilimumab will be administered at a dose of 1 mg/kg. Each treatment cycle will be 3 weeks in length. BMS-986178 will be administered q3w starting on Cycle 1 Day 1, up to and including 8 cycles, and ipilimumab will be administered q3w starting on Day 1 for 4 cycles. Only BMS-986178 will be administered in the last 4 cycles.

3.1.2.4 BLRM Dose Escalation and Stopping Rules

In Parts 1A, 2A, and 3A, the BLRM and BLRM (-Copula) models (Section 1.1.15) will be utilized for dose escalation recommendations after DLT information becomes available for each cohort of subjects. BMS-986178 dose selection for the next cohort/dose level will take into account the BLRM (-Copula) recommendation in conjunction with clinical recommendation and all available PK, PD, and clinical and laboratory safety data from all treated subjects. The final dose escalation decision will be made after discussion and agreement between investigators and the BMS Medical Monitor.

BLRM Dose Escalation Rules (Parts 1A, 2A, and 3A)

Cohort tolerability assessment and subsequent dose recommendation will occur when 2 evaluable subjects within a dose cohort have completed the 28-day DLT period. If the potential DLT occurring in the third evaluable subject at a specific dose level does not influence the dose recommendation by BLRM (-Copula), the BLRM (-Copula)-recommended next dose level may proceed without waiting for the third subject to complete the corresponding DLT observation period after discussion and agreement between the Sponsor and investigators. While waiting for the DLT information of those 2 or 3 subjects, if additional subjects are available, these subjects could be enrolled to the current dose level. Continuous re-assessment of dose recommendation by BLRM (-Copula) will be carried out at every dose level of each cohort of subjects, taking into consideration all available DLT information.

The BLRM (-Copula) model will first exclude doses that are intolerable (with overdosing probabilities > 25%). Among those qualified candidate doses that are considered “safe”, the model will select the dose that maximizes the probability of being within the target toxicity range (DLT rate of 16% to up to 33%).

- Dose levels for the next cohort will be based on evaluating 4 potential recommendations: escalate, de-escalate, stay at same dose level, or stop and select a new dose other than pre-specified doses.
- Escalation by more than 1 dose level (dose skipping) is not permitted.

- Based on model suggestions and a review of the available safety, PK, and PD data in combination with clinical recommendation, lower doses of BMS-986178 may be tested if none of the planned doses are found to be tolerated as monotherapy or in combination with nivolumab or ipilimumab. Such decisions will be made after discussion and agreement between the investigators and the BMS Medical Monitor.
- No intra-subject dose escalation of BMS-986178 is allowed at any dose level.
- Dose de-escalation can be recommended by the model, and the final decision will be made based on clinical recommendation.

BLRM Stopping Rules during Dose Escalation (Parts 1A, 2A, and 3A)

- If all of the current pre-specified doses are considered intolerable according to the pre-specified cutoff, then the model will recommend stopping the current dose level and a new dose level lower than the current lowest dose level will need to be identified (EWOC stopping).
- The maximum number of subjects in a dose level will be 12. This limit is set to avoid instances in which the model could recommend adding subjects indefinitely to a specific dose level due to uncertainty in the tolerability profile.
- If, for a specific dose level, 6 subjects have been treated and the chance of determining that dose level to be the "target" dose is > 50%, then the model will suggest to stop the arm and declare the current dose level to be MTD.

Appendix 1 provides further detailed explanation along with an illustration of the BLRM dose escalation design.

3.1.2.5 Dose-Limiting Toxicity in Dose Escalation Parts

For the purpose of guiding dose escalation, DLTs will be defined based on the incidence, severity, and duration of AEs for which no clear alternative cause is identified. The DLT period will be 28 days after initial dosing in monotherapy and combination parts of dose escalation.

For the purpose of defining MTD/RP2D, the incidence of DLTs during the DLT period will be used. AEs occurring after the DLT period will be considered for the purposes of defining the RP2D upon agreement between the Sponsor, Medical Monitor, and investigators, if they are determined to have no clear alternative cause and are not related to disease progression.

For the purpose of subject management, any AE that meets DLT criteria, regardless of the cycle in which it occurs, will lead to discontinuation of study drug. Subjects experiencing a DLT will not be retreated with study drug(s) and will enter the Safety Follow-up period of the study for up to 100 days from the last administration of the study drug(s). Subjects who withdraw from the study during the DLT evaluation interval for reasons other than a DLT may be replaced with a new subject at the same dose level.

Further details on DLTs are included in Section 4.5.1.

3.1.3 Schedule and Dose Exploration

3.1.3.1 Part 4: Combination with Nivolumab on a 4-week Schedule

Part 4 is the combination arm of BMS-986178 with nivolumab (480 mg) to be administered q4w. The dose of BMS-986178 will be a dose previously evaluated in Part 2A that has been found to have a manageable safety profile. If the starting dose of BMS-986178 is not tolerated or to further characterize the dose response for safety, PK, or PD as appropriate based on clinical data collected, a dose(s) lower or higher than the previously administered dose in this part may be explored. To further ensure safety of the combination, at no time will the dose for BMS-986178 in Part 4 exceed the highest tolerated dose in Part 2A, in which q2w dosing is explored. Approximately 6 to 12 subjects will be treated in this schedule and dose exploration cohort.

3.1.3.2 Part 5: Combination with Ipilimumab at 3 mg/kg

Part 5 is the combination arm of BMS-986178 with ipilimumab 3 mg/kg q3w for 4 doses, followed by monotherapy with BMS-986178 (maintenance therapy). The dose of BMS-986178 will be a dose previously evaluated in Part 3A that has been found to have a manageable safety profile. If the starting dose of BMS-986178 is not tolerated or to further characterize the dose response for safety, PK, or PD as appropriate based on clinical data collected, a dose(s) lower or higher than the previously administered dose in this part may be explored. To further ensure safety of the combination, at no time will the dose for BMS-986178 in Part 5 exceed the highest tolerated dose in Part 3A. Approximately 6 to 12 subjects will be treated in this schedule and dose exploration cohort.

3.1.3.3 Part 8: Dose Regimen Exploration of Combination with Nivolumab in Bladder Cancer

Part 8 is a dose regimen exploration of BMS-986178 in combination with nivolumab or nivolumab monotherapy. Nivolumab will be administered at a flat dose of 480 mg to be administered every 4 weeks.

Approximately 20 evaluable subjects per cohort will be treated in Part 8.

Part 8 Cohort 1-3: BMS-986178 will be administered as a flat dose of either 20 mg, 40 mg, or 80 mg q12w in combination with nivolumab flat dose (480 mg; q4w). Each treatment cycle will be 12 weeks in length starting on Day 1 of each cycle. There will be up to 9 cycles, to allow for 24 months of treatment. A tetanus vaccine (Tdap preferred, Td or equivalent after discussion with the medical monitor) will be administered first on Cycle 1 Day 1 prior to administration of nivolumab and BMS-986178.

Part 8 Cohort 4: Nivolumab monotherapy will be administered as a flat dose of 480 mg (q4w). Each treatment cycle will be 12 weeks in length and will be dosed for up to 9 cycles, 24 months of dosing. Treatment will be given on Day 1, Day 29 and 57 of each cycle. A tetanus vaccine (Tdap preferred, Td or equivalent after discussion with the medical monitor) will be administered first on Cycle 1 Day 1 prior to administration of nivolumab monotherapy.

3.1.3.4 Part 9 Combination BMS-986178, Nivolumab, and DPV-001

In part 9, subjects will be randomized in a 2:1 ratio to cohort 1 or cohort 2.

Part 9 Cohort 1

Cohort 1 is a combination of BMS-986178, nivolumab, DPV-001 (UbiLT3 and UbiLT6) vaccine, and single dose cyclophosphamide. Single-dose cyclophosphamide 300 mg/m^2 is to be administered IV over a 30 to 60 minute infusion, 3 days prior to C1D1. On C1D1 the subjects will receive both UbiLT3 and UbiLT6 IN by ultrasound guidance. DPV-001 on C1D1 will consist of both UbiLT3 and UbiLT6 vaccine (total of 1.0 mL suspension, 0.5 mL suspension UbiLT3 into 1 lymph node and 0.5 mL of UbiLT6 into another lymph node). After the DPV-001 is administered on C1D1, the subject will be administered BMS-986178, as a flat dose of 40 mg (q4w) over a 30-minute infusion. The order of dose administration is DPV-001 then BMS-986178 for C1D1.

On day C1D8, the subject will be administered both UbiLT3 and UbiLT6, at the same dose listed on C1D1, but it will be administered ID.

On C1D15, the subject with be administered UbiLT3 ID which will then commence alternating between UbiLT3 and UbiLT6 on subsequent doses, then the subject will be administered nivolumab at 240 mg infusion over 30 minutes. BMS-986178 will only be given on day 1 of cycles 1-6, 9, and 12.

DPV-001 vaccine will be given as a total of 1 mg flat dose at each administration. Vaccine may be given as multiple injections due to volume, according to institutional policy.

Subsequent doses of DPV-001 are delivered ID q2w (1.0 mL suspension ID rotating between UbiLT3 and UbiLT6 on alternate vaccinations, starting with UbiLT3) which starts at C1D15 for a total of 4 doses. From C3D1 to C6D1, subjects will receive this vaccine q4w, (still alternating between the UbiLT3 and UbiLT6). After cycle 6, the vaccine will be given 2 more times, at C9D1 and C12D1 (still alternating between the UbiLT3 and UbiLT6).

From C2D1 through C6D1, nivolumab will be administered as a 480 mg flat dose q4w. It will be administered as an infusion over a 30-minute period, after DPV-001 is given. BMS-986178 will be administered following a 30-minute waiting period after the nivolumab dosing. Nivolumab will continue to be administered as a 480 mg flat dose q4w. At C7D1, C8D1, C10D1, C11D1 and C13D1 to C26D1, nivolumab will be given as a monotherapy dose.

Approximately 12 subjects will be treated in this cohort. All cycles will be 4 weeks in length.

Part 9 Cohort 2

Cohort 2 is a combination of nivolumab, DPV-001 (UbiLT3 and UbiLT6) vaccine, and single dose cyclophosphamide. Single-dose cyclophosphamide 300 mg/m^2 is to be administered IV over a 30 to 60 minute infusion, 3 days prior to C1D1. On C1D1 the subjects will receive DPV-001 IN by ultrasound guidance. DPV-001 on C1D1 will consist of both UbiLT3 and UbiLT6 vaccine (total of 1.0 mL suspension, 0.5 mL suspension UbiLT3 into one lymph node and 0.5 mL of UbiLT6 into another lymph node).

On day C1D8, the subject will be administered both UbiLT3 and UbiLT6, at the same dose level above, but it will be administered ID.

On C1D15, the subject will be administered UbiLT3 ID which will then commence alternating between UbiLT3 and UbiLT6 on subsequent doses. Then the subject will be administered nivolumab at 240 mg infusion over 30 minutes on C1D15.

DPV-001 vaccine will be given as a total of 1 mg flat dose at each administration. Vaccine may be given as multiple injections due to volume, according to institutional policy.

Subsequent doses of DPV-001 are delivered ID q2w (1.0 mL suspension ID rotating between UbiLT3 and UbiLT6 on alternate vaccinations, starting with UbiLT3), which starts at C1D15 for a total of 4 doses. From C3D1 to C6D1, subjects will receive this vaccine q4w, still alternating between the UbiLT3 and UbiLT6). After cycle 6, the vaccine will be given 2 more times, at C9D1 and C12D1.

Beginning at C2D1 through C26D1, nivolumab will be administered as a 480 mg flat dose q4w on Day 1 of each cycle, as an infusion over a 30-minute period. When nivolumab and DPV-001 are given together, DPV-001 will be given first.

Approximately 6 subjects will be treated in this cohort. All cycles will be 4 weeks in length.

One sentinel subject will be dosed initially in each cohort in Part 9, prior to dosing of subsequent subjects. The sentinel subject will be observed for 5 days before the next subject is dosed. If cytokine release syndrome or unexpected toxicity occurs in the first treated subject during the sentinel observation period, subsequently 2 subjects will be treated sequentially, with an interval period of at least 5 days between the beginning of treatment for patient 2 and 3. If cytokine release syndrome is observed in 2 of the first 3 treated subjects, then the regimen and/or schedule will be re-evaluated, with consideration for lower doses of study drug(s) before additional subjects are enrolled.

3.1.4 Safety Cohorts

3.1.4.1 Part 6A: Combination with Nivolumab and Ipilimumab in RCC

Part 6A is the safety cohort for the combination of BMS-986178 with ipilimumab and nivolumab in subjects with RCC. BMS-986178 will be administered at a flat dose of 40 mg in combination with nivolumab (240 mg) and ipilimumab (1 mg/kg) q3w during Cycles 1 to 4, followed by maintenance therapy (Cycle 5 and beyond) in which BMS-986178 (40 mg) and nivolumab (480 mg) will be administered q4w. Study drugs will be administered accordingly starting on Day 1 of each cycle. If the starting dose of BMS-986178 is not tolerated or to further characterize the dose response for safety, PK, or PD as appropriate based on clinical data collected, a dose(s) lower than the previously administered dose in this part may be explored. Approximately 6 to 12 subjects will be treated in this safety cohort.

3.1.4.2 Part 7A: Combination with Nivolumab and Ipilimumab in NSCLC

Part 7A is the safety cohort for the combination of BMS-986178 with ipilimumab and nivolumab in subjects with NSCLC. BMS-986178 will be administered at a flat dose of 40 mg (q2w) in

combination with nivolumab (240 mg; q2w) and ipilimumab (1 mg/kg; q6w) for four 6-week cycles. Study drugs will be administered accordingly starting on Day 1 of each cycle. If the starting dose of BMS-986178 is not tolerated or to further characterize the dose response for safety, PK, or PD as appropriate based on clinical data collected, a dose(s) lower than the previously administered dose in this part may be explored. If subjects continue for additional cycles, past cycle 4, all study drugs (BMS-986178/nivolumab/ipilimumab) will continue for all cycles. Approximately 6 to 12 subjects will be treated in this safety cohort.

3.1.5 Dose Expansion Parts (Parts 2B, 2C, 2D, 2E, 3B, 3C, 6B, 7B)

Treatment in the dose expansion cohorts will be initiated when the MTD/RP2D(s) has been determined based on the evaluation of totality of available clinical safety (DLTs, AEs occurring after the DLT period), PK, PD, immunogenicity, and modeling data from the dose escalation parts (1A, 2A, and 3A) or schedule and dose exploration parts (4 and 5). Mandatory pre- and on-treatment biopsies of tumor will be obtained for all study subjects.

3.1.5.1 Part 2B: Combination with Nivolumab Dose Expansion in Colorectal Cancer

Part 2B is the combination therapy (BMS-986178 with nivolumab) dose expansion part in subjects with CRC at the MTD/RP2D(s) determined in Parts 2A or 4. Nivolumab will be administered at a flat dose of 240 or 480 mg. Each treatment cycle will be either 2 (240 mg) or 4 (480 mg) weeks in length and study drugs will be administered every 2 or 4 weeks starting on Day 1 of each cycle for up to 12 or 6 cycles, respectively. Approximately 35 subjects will be treated in this expansion cohort.

3.1.5.2 Part 2C: Combination with Nivolumab Dose Expansion in Bladder Cancer

Part 2C is the combination therapy (BMS-986178 with nivolumab) dose expansion part in subjects with BC at the MTD/RP2D(s) determined in Parts 2A or 4. Nivolumab will be administered at a flat dose of 240 or 480 mg. Each treatment cycle will be either 2 (240 mg) or 4 (480 mg) weeks in length and study drugs will be administered every 2 or 4 weeks starting on Day 1 of each cycle for up to 12 or 6 cycles, respectively. Approximately 27 subjects will be treated in this expansion cohort.

3.1.5.3 Part 2D: Combination with Nivolumab Dose Expansion in Cancer of the Cervix

Part 2D is the combination therapy (BMS-986178 with nivolumab) dose expansion part in subjects with cervical cancer at the MTD/RP2D(s) determined in Part 2A or 4. Nivolumab will be administered at a flat dose of 240 or 480 mg. Each treatment cycle will be either 2 (240 mg) or 4 (480 mg) weeks in length and study drugs will be administered every 2 or 4 weeks starting on Day 1 of each cycle for up to 12 or 6 cycles, respectively. Approximately 37 subjects will be treated in this expansion cohort.

3.1.5.4 Part 2E: Combination with Nivolumab Dose Expansion in Other Tumors for Signal Finding

Part 2E is the combination therapy (BMS-986178 with nivolumab) dose expansion part at the MTD/RP2D(s) determined in Part 2A or 4. Nivolumab will be administered at a flat dose of 240 or 480 mg. Each treatment cycle will be either 2 (240 mg) or 4 (480 mg) weeks in length and study drugs will be administered every 2 or 4 weeks starting on Day 1 of each cycle for up to 12 or 6 cycles, respectively. Approximately 40 subjects will be treated in this expansion cohort.

Tumor types for this cohort will be selected by Sponsor from those permitted in dose escalation which do not have a dedicated expansion cohort or plans for evaluation in other studies and those tumors selected will be communicated to the investigators. This cohort will allow for further exploration of early signs of clinical activity observed in tumors during the dose escalation phase of the trial as well as potential signals arising from ongoing trials of other anti-OX40 agonists in combination with anti-PD(L)-1. Subjects enrolled in this cohort must be refractory to or intolerant of established therapy known to provide clinical benefit for their condition, i.e., subjects must not be candidates for regimens known to provide clinical benefit.

3.1.5.5 Part 3B: Combination with Ipilimumab Dose Expansion in Ovarian Cancer

Part 3B is the combination therapy (BMS-986178 with ipilimumab) dose expansion part in subjects with OC at the MTD/RP2D(s) determined in Part 3A or 5. Each treatment cycle will be 3 weeks in length. Ipilimumab will be administered in the initial 4 cycles in combination with BMS-986178. Then the subject will continue on BMS-986178 monotherapy for up to an additional 4 cycles for a total of up to 24 weeks (8 cycles) of treatment. Approximately 35 subjects with OC will be treated in this expansion cohort.

3.1.5.6 Part 3C: Combination with Ipilimumab Dose Expansion in Other Tumors for Signal Finding

Part 3C is the combination therapy (BMS-986178 with ipilimumab) dose expansion part in subjects with other tumors from dose escalation for signal finding at the MTD/RP2D(s) determined in Part 3A or 5. Each treatment cycle will be 3 weeks in length. Ipilimumab will be administered in the initial 4 cycles in combination with BMS-986178. Then the subject will continue on BMS-986178 monotherapy for up to an additional 4 cycles for a total of up to 24 weeks (8 cycles) of treatment. Approximately 40 subjects will be treated in this expansion cohort.

Tumor types for this cohort will be selected by Sponsor from those permitted in dose escalation which do not have a dedicated expansion cohort or plans for evaluation in other studies and those selected tumors will be communicated to the investigators. This cohort will allow for further exploration of early signs of clinical activity observed in tumors during the dose escalation phase of the trial as well as potential signals arising from ongoing trials of other anti-OX40 agonists in combination with anti-CTLA-4. Subjects enrolled in this cohort must be refractory to or intolerant of established therapy known to provide clinical benefit for their condition, i.e., subjects must not be candidates for regimens known to provide clinical benefit.

3.1.5.7 Part 6B: Combination with Nivolumab and Ipilimumab in Renal Cell Carcinoma

Part 6B is the combination therapy (BMS-986178, nivolumab, and ipilimumab) dose expansion part in subjects with RCC at a dose determined to be tolerated in Part 6A. BMS-986178 will be administered at the RP2D(s) in combination with nivolumab (240 mg) and ipilimumab (1 mg/kg) q3w during Cycles 1 to 4 followed by maintenance therapy (Cycle 5 and beyond) in which BMS-986178 and nivolumab (480 mg) will be administered q4w. Study drugs will be administered accordingly starting on Day 1 of each cycle. Approximately 40 subjects will be treated in this expansion cohort.

3.1.5.8 Part 7B: Combination with Nivolumab and Ipilimumab in Non-small Cell Lung Cancer

Part 7B is the combination therapy (BMS-986178, nivolumab, and ipilimumab) dose expansion part in subjects with NSCLC at a dose determined to be tolerated in Part 7A. BMS-986178 will be administered at the RP2D(s) (q2w) in combination with nivolumab (240 mg; q2w) and ipilimumab (1 mg/kg; q6w) for four, 6-week cycles. Study drugs will be administered accordingly starting on Day 1 of each cycle. If subjects continue for additional cycles, past Cycle 4, all study drugs (BMS-986178/nivolumab/ipilimumab) will continue for all cycles. Approximately 40 subjects will be treated in this expansion cohort.

3.1.5.9 Stopping Rules during Dose Expansion

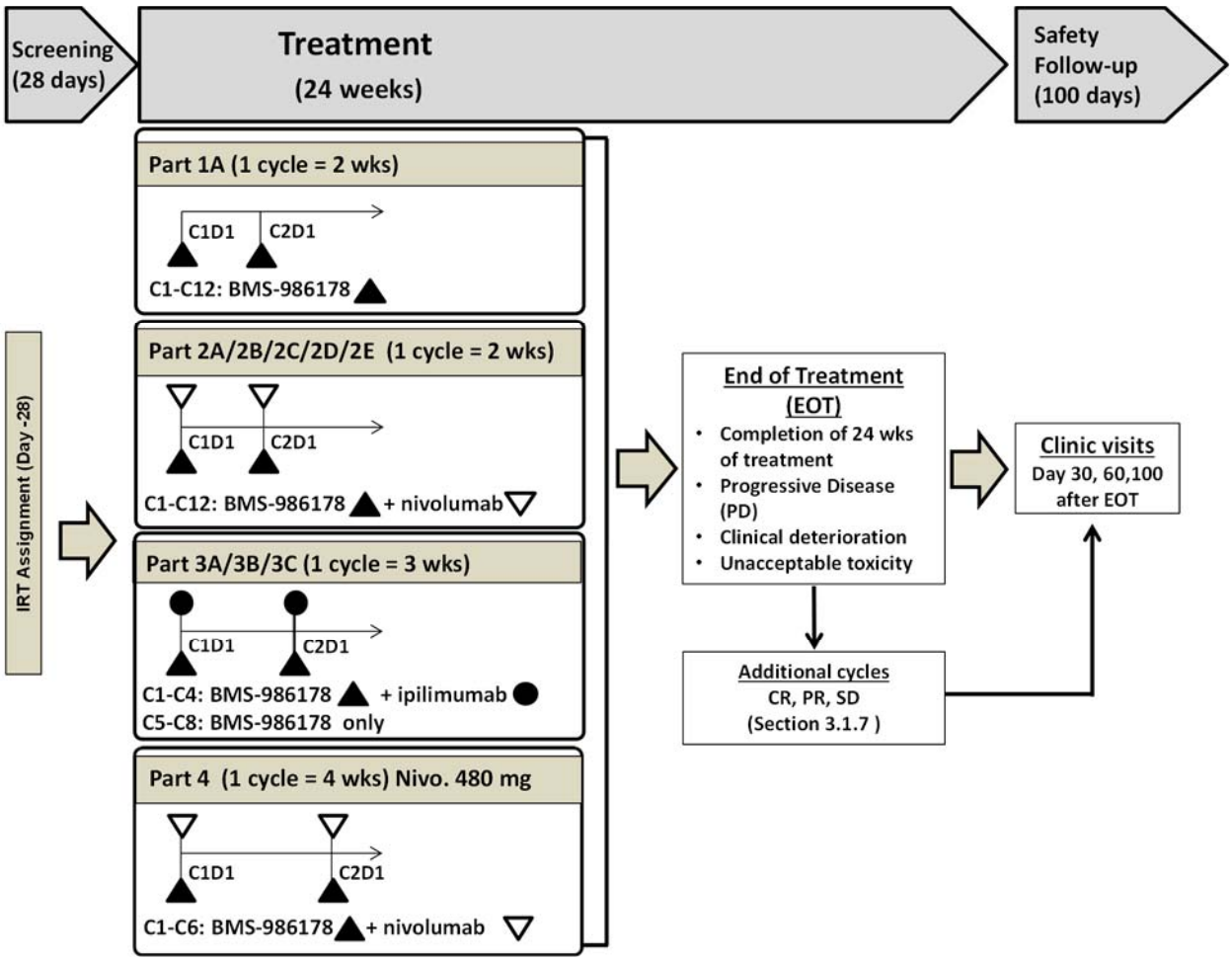
- Evaluation of toxicity will be performed throughout enrollment in the dose expansion cohorts.
- If the rate of DLTs exceeds 33% in any cohort, the findings will be discussed between the investigators and Sponsor, and further enrollment may be interrupted in that expansion cohort.
- If an expansion cohort is discontinued due to toxicity, a new cohort at a previously tested lower dose level may be considered based on the aggregate safety experience and in consultation and agreement between the investigators and Sponsor.
- During dose expansion, a specific cohort may be stopped due to lack of efficacy per Simon 2-stage design recommendation.[176,177] Due to the heterogeneous nature of tumor responses seen with immunotherapy (eg, late responses), such a decision would not be strictly based on the number of responses but would include all available efficacy data.
- The non-binding nature of stopping boundaries allows for flexibility of examination on the totality of data to determine the risk/benefit ratio.

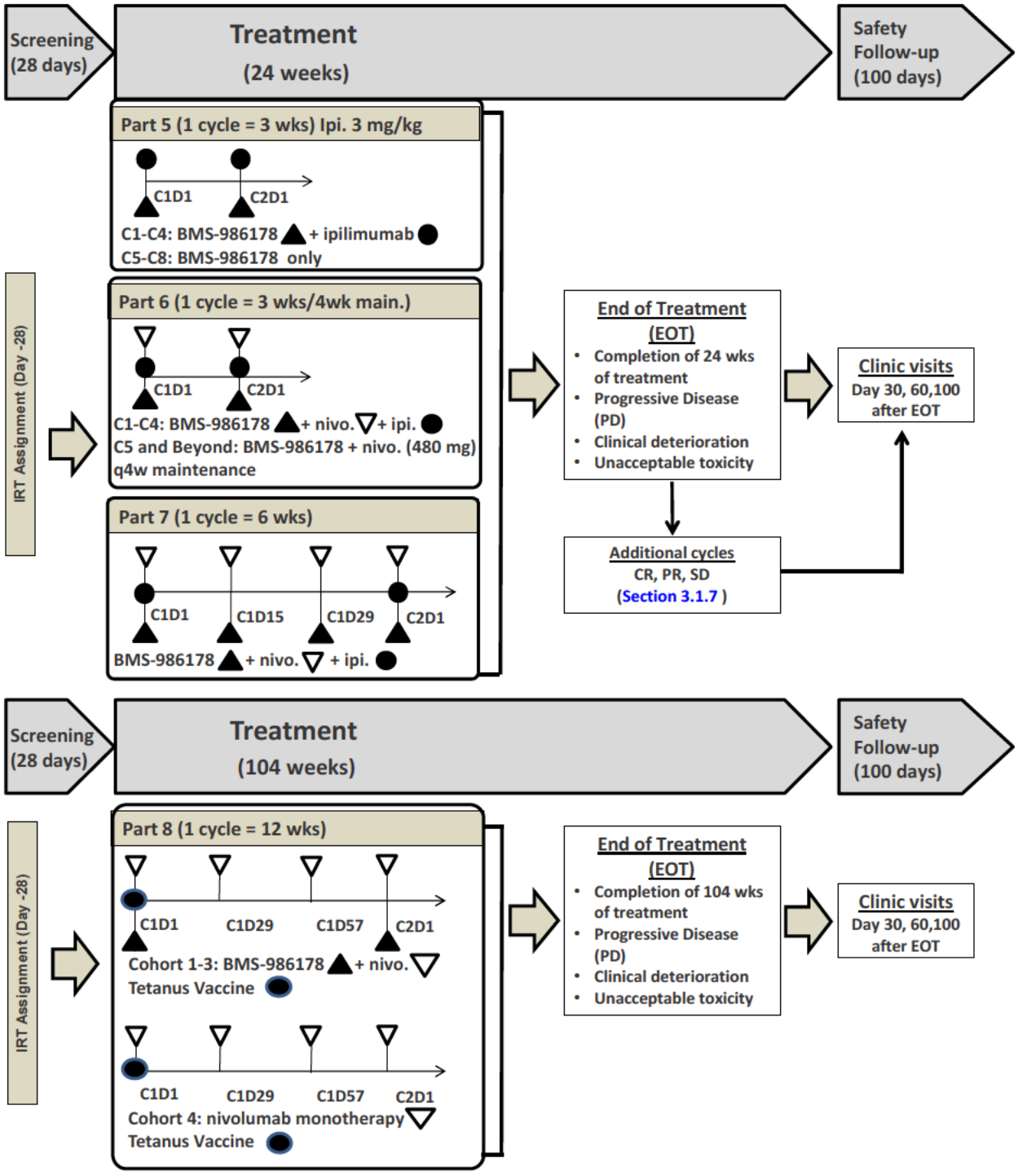
3.1.6 Study Schedule

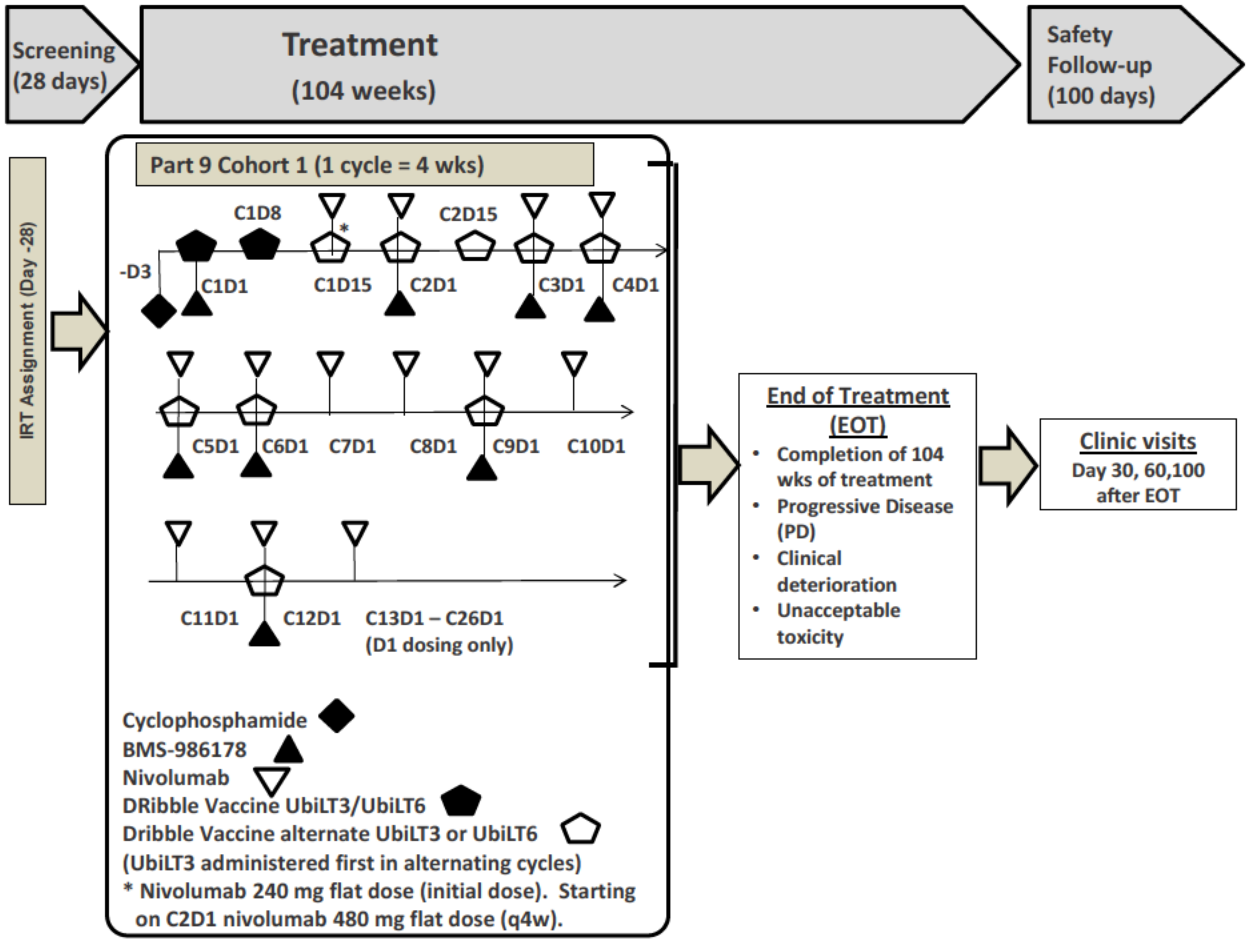
In all cohorts, subjects will complete: Screening (up to 28 days), Treatment (up to 24 weeks [Parts 1-7], until meeting protocol-specified discontinuation criteria), and Safety Follow-up (approximately 100 days), as described below. Screening and the Treatment period are calculated relative to the first dose of study drug, while Safety Follow-up periods are calculated relative to the last dose. The study visit schematic is presented in Figure 3.1.6-1. The study will end when the last subject completes their last study visit, which is planned to be about 4 years after the start of the study. Parts 8 and 9 subjects will receive treatment up to 24 months (the maximum treatment

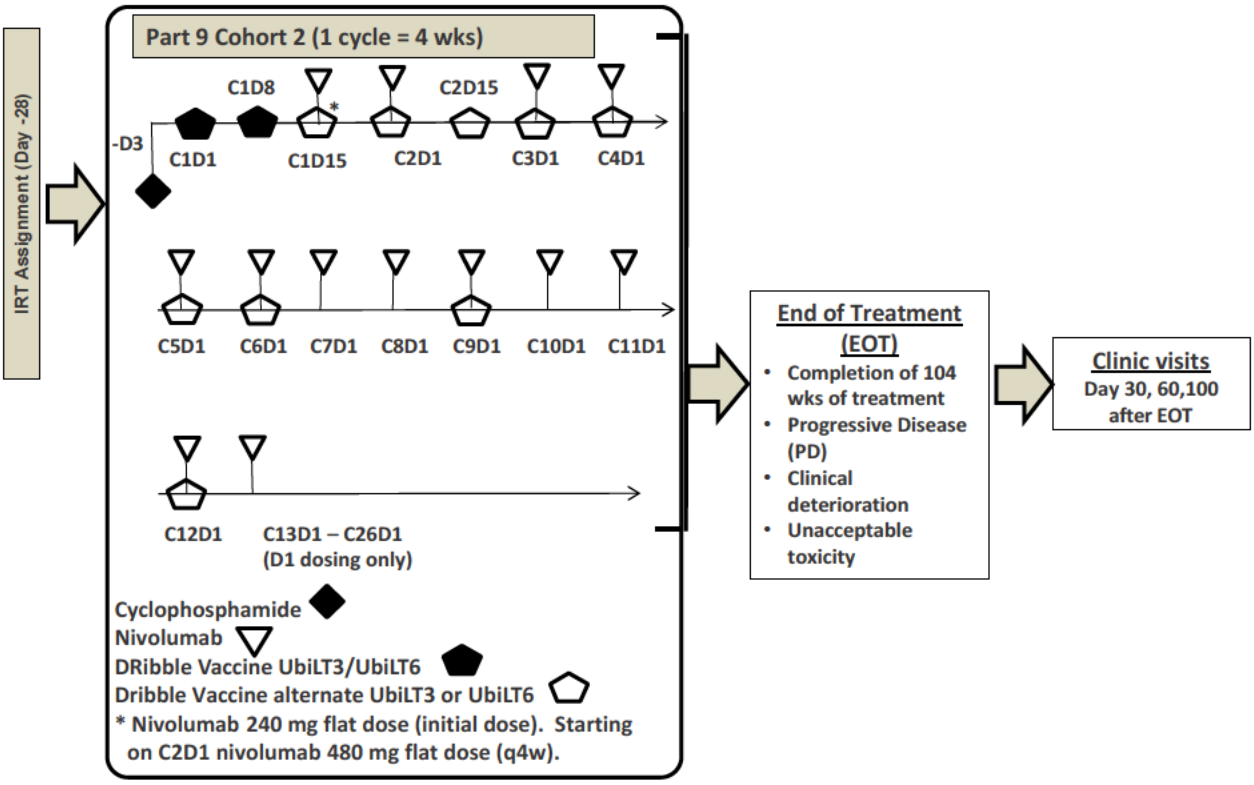
allowed for any subject is 2 years from the first dose of study treatment regardless of dose delays). Safety Follow-up period will be approximately 100 days from the end of treatment.

Figure 3.1.6-1: Study Visit Schematic









Abbreviations: CR = complete response; EOT = end of treatment; Ipi = ipilimumab; IRT = Interactive Response Technology; Nivo = nivolumab; PD = progressive disease; PR = partial response; SD = stable disease; wks = weeks.

3.1.6.1 Screening Period

The screening period will last for up to 28 days. The screening period begins by establishing the subject's initial eligibility and signing of the ICF. Subjects will be enrolled using an Interactive Response Technology (IRT).

If a subject surpasses the 28-day window during the screening period due to a study-related procedure (eg, scheduling of a tumor biopsy or waiting time for a study-related laboratory value), the subject must be re-consented, but does not need to be assigned a new subject identification number. In this situation, the fewest number of procedures from the initial screening should be repeated to qualify the subject, while maintaining safety and eligibility under the discretion of the BMS Medical Monitor and investigator, to reduce any undue burden of procedures in this subject population.

In the instance of a SARS-CoV-2 infection during screening, the screening period may be extended beyond the protocol-specified timeframe with documented medical monitor approval. Any screening tests already performed which could potentially be affected by the SARS-CoV-2 infection or its complications on an individual basis and agreed upon with the medical monitor (eg, safety labs, pulse oximetry, chest CT scan) should be repeated.

3.1.6.2 Treatment Period

Eligible subjects will be assigned to the open parts/cohorts by IRT (see Section 4.4). Subjects must meet all eligibility criteria at time of treatment initiation.

The treatment period consists of up to 24 weeks of dosing for Parts 1-7. Parts 8 and 9 will have a treatment period up to a maximum of 24 months of dosing from first dose regardless of treatment delays.

Following each treatment cycle, the decision to treat a subject with the next cycle of study therapy, up to 24 weeks of treatment or in Parts 8 and 9 up to 24 months, will be based on risk/benefit and tumor assessments. Tumor assessments will be performed every 8 weeks for Parts 1-7 and 9 or every 12 weeks for Part 8 (± 1 week). Assessments of partial response (PR) and complete response (CR) must be confirmed at least 4 weeks following initial assessment. Tumor progression or response endpoints will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 3).

Subjects with a response of SD, PR, or CR at the end of a given cycle will continue to the next treatment cycle. Subjects will generally be allowed to continue study therapy until the first occurrence of one of the following: 1) completion of the maximum number of cycles; 2) PD; 3) clinical deterioration suggesting that no further benefit from treatment is likely; 4) intolerability to therapy; or 5) the subject meets criteria for discontinuation of study therapy as outlined in Section 4.5.6. Individual subjects with confirmed CR will be given the option to discontinue study therapy on a case-by-case basis after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where risk/benefit justify discontinuation of study therapy.

Approximately 642 subjects will be enrolled, and approximately 545 subjects will be treated in the study.

3.1.6.3 Safety Follow-up

Upon completion of study therapy, subjects will enter the Safety Follow-up period.

After the end of treatment (EOT) visit, subjects will be evaluated for any new AEs for at least 100 days after the last dose of therapy. Follow-up visits should occur at Days 30, 60, and 100 after the last dose or the date of discontinuation. Subjects (except those who withdraw consent for study participation) are expected to complete the 3 clinical Safety Follow-up visits regardless of whether they start new anti-cancer therapy.

For subjects who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit, and the start of Week 1 Safety Follow-up visit. For subjects who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data); the visit does not need to be repeated and will be considered the start of the Safety Follow-up period.

3.1.7 Treatment with Additional Cycles

Parts 1-7 subjects will be treated for 24 weeks unless criteria for study drug discontinuation are met earlier (Section 4.5.6). Subjects in Parts 2, 4, 6, and 7 completing approximately 24 weeks of

treatment with ongoing disease control (CR, PR, or SD) may be eligible for an additional 18 months of study therapy beyond the initial 24 weeks, on a case-by-case basis, after discussion and agreement with the BMS Medical Monitor that the risk/benefit assessment favors continued administration of study therapy. Upon completion of the additional 18 months of study therapy, subjects will enter Safety Follow-up period. Parts 8 and 9 subjects will not be eligible for treatment with additional cycles. The maximum treatment allowed for any subject is 2 years from the first dose of study treatment regardless of dose delays.

Parts 3 and 5 subjects completing approximately 24 weeks of treatment with ongoing disease control (CR, PR, or SD) may be eligible for an additional 24 weeks of study therapy beyond the initial 24 weeks, on a case-by-case basis, after discussion and agreement with the BMS Medical Monitor that the risk/benefit assessment favors continued administration of study therapy. Upon completion of the additional 24 weeks of study therapy, subjects will enter Safety Follow-up period.

3.1.8 Treatment Beyond Progression

Treatment beyond progression may be allowed in select subjects with initial RECIST v1.1-defined progressive disease after discussion and agreement with the BMS Medical Monitor that the benefit/risk assessment favors continued administration of study therapy (eg, subjects are continuing to experience clinical benefit as assessed by the investigator, tolerating treatment, and meeting other criteria specified in Section 3.5.1.

Subjects must be re-consented with an Informed Consent Form addendum to continue treatment beyond progression.

3.2 Post-study Access to Therapy

At the end of the study, BMS will not continue to provide BMS-supplied study drug to subjects and investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate SOC to treat the condition under study.

3.3 Study Population

For entry into the study, the following criteria MUST be met prior to dosing on Day 1. No exceptions will be granted.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent
   a) Participants or their legally acceptable representative, must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.
   b) Consent for tumor biopsy samples (mandatory pre- and on-treatment biopsies) are required for all subjects enrolled.
   c) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.
2) Type of Participant and Target Disease Characteristics

Subjects must be at least 18 years old and have histologic or cytologic confirmation of a malignancy that is advanced (metastatic, recurrent, refractory, and/or unresectable) with measurable disease per RECIST v1.1 (see Appendix 3).

1) **Dose Escalation/Schedule and Dose Exploration/Safety Cohorts/Dose Expansion (Part 2E/3C)** Subjects must be refractory to or intolerant of established therapy known to provide clinical benefit for their condition, i.e., subjects must not be candidates for regimens known to provide clinical benefit.

   The following tumor histologies will be permitted except for subjects with primary central nervous system (CNS) tumors, or with CNS metastases as the only site of active disease.

   Parts 1A, 2A, 2E, 3A, 3C, 4, and 5

   (i) Melanoma: BRAF mutation status must be documented if known

   (ii) NSCLC: EGFR, anaplastic lymphoma kinase (ALK), KRAS, and ROS1 mutational status must be documented if known

   (iii) Head and neck cancer restricted to squamous cell carcinoma: HPV status must be documented if known

   (iv) Transitional cell carcinoma of the genitourinary tract

   (v) Renal cell carcinoma

   (vi) Pancreatic adenocarcinoma

   (vii) CRC: MSI, KRAS, and BRAF status must be documented if known

   (viii) Cervical cancer: HPV status must be documented if known

   (ix) Triple negative breast cancer HER2, ER, and PgR status must be documented

   (x) Adenocarcinoma of the endometrium

   (xi) Ovarian cancer

   (xii) Prostate adenocarcinoma

   (xiii) Hepatocellular cancer-Child Pugh A only

   (xiv) Small cell lung cancer

   (xv) Gastric and gastric esophageal junction cancer: HER2 status must be documented if known

   (xvi) Thyroid cancer

   Part 6A (RCC)

   (xvii) Subjects with histological confirmation of RCC with a clear-cell component

   (xviii) Subjects must have received at least 1, but no more than 2, prior systemic therapies in the advanced/metastatic setting.

Part 7A (NSCLC)

Subjects must have histologic or cytologic confirmation of NSCLC (per the seventh International Association for the Study of Lung Cancer [IASLC][178]) with squamous or nonsquamous histology that is advanced (metastatic and/or unresectable).

(xix) Subjects must have had at least 1, but no more than 2, prior systemic therapies for NSCLC. Maintenance, adjuvant, or neoadjuvant (chemotherapy or chemoradiation) therapy does not count as an additional line of treatment.

(xx) Subjects should have been offered a platinum-based chemotherapy for NSCLC. The platinum-based chemotherapy may have been in the adjuvant, neoadjuvant, or recurrent setting. Prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least 4 weeks prior to enrollment.

(xxi) Prior definitive chemoradiation for locally advanced disease is also permitted as long as the last administration of chemotherapy or radiotherapy (whichever was given last) occurred at least 4 weeks prior to enrollment.

(xxii) Subjects with known EGFR mutations or ALK rearrangements must have received EGFR or ALK inhibitors, respectively.

(xxiii) EGFR, ALK, KRAS, ROS1 mutational status must be documented if known.

2) **Dose Expansion: Parts 2B, 2C, 2D, 3B, 6B, 7B, 8, and 9**

The following tumor types will be permitted:

(a) Cervical Cancer - Part 2D

(i) Histologically confirmed cervical cancer that is unresectable, metastatic, or recurrent with documented disease progression

(ii) Document tumor HPV status if known. If tumor HPV status is unknown, subjects must consent to allow their submitted archived tumor tissue sample (block or unstained slides) to be tested.

(iii)Prior therapy requirement:

Subjects must have been offered and/or have received or refused at least 1 prior platinum-based therapy for metastatic and/or unresectable disease. Subjects must have not received more than 2 prior systemic therapies. Reason(s) for refusal should be documented. Concurrent chemotherapy administered with primary radiation and adjuvant chemotherapy given following completion of radiation therapy do not count as systemic therapies, though patients who progressed less than 6 months from primary platinum-based therapy are eligible.

(b) Colorectal Cancer - Part 2B

(i) Histologically confirmed CRC that is metastatic or recurrent with documented disease progression

(ii) Document MSI, MMR, KRAS, and BRAF status if known. If unknown, subjects must consent to allow their submitted archived tumor tissue sample (block or unstained slides) to be tested.

(iii) Prior therapy requirement:

Subjects must have received at least 1, but no more than 3, prior systemic therapies for metastatic and/or unresectable disease (or have progressed within 6 months of adjuvant therapy).

(c) Bladder Cancer - Part 2C

(i) Histologically or cytologically confirmed urothelial carcinoma (including mixed histologies of urothelial carcinoma with elements of other subtypes) of the renal pelvis, ureter, bladder, or urethra with progression or refractory disease

(ii) Prior therapy requirement:

Subjects must have been offered and/or have received or refused 1 prior platinum-based therapy for the treatment of metastatic or locally advanced unresectable disease. Subjects must have not received more than 2 prior systemic therapies. Reason(s) for refusal should be documented.

(d) Ovarian - Part 3B

(i) Histologically or cytologically confirmed ovarian carcinoma (including epithelial OC, primary peritoneal, or fallopian tube carcinoma) with documented disease progression

(ii) Documented germline BRCA mutation status, if known. If unknown, subjects must consent to allow their submitted archived tumor tissue sample (block or unstained slides) to be tested.

(iii) Prior therapy requirement:

Subjects must have received no more than 3 prior systemic therapies. One regimen must have been a prior platinum-based chemotherapy regimen for primary disease, possibly including intra-peritoneal therapy consolidation, biologic/targeted (non-cytotoxic) agents, or extended therapy (maintenance/consolidation) administered after surgical or non-surgical assessment. Patients must have progressed less than 12 months after completion of their last platinum-based chemotherapy. The number of months (platinum-free interval) should be calculated from the date of the last administered dose of platinum therapy to the date of the documentation of progression.

(e) RCC (Part 6B)

(i) Subjects with histologically confirmed RCC with a clear-cell component

(ii) Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC

(iii) No prior systemic therapy for RCC with the following exception:

One prior adjuvant or neoadjuvant therapy for completely resectable RCC if such therapy did not include an agent that targets VEGF or VEGF receptors and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy.

(iv) Subjects with favorable-, intermediate-, and poor-risk categories will be eligible for the study. Subjects must be categorized according to favorable- versus intermediate-/poor-risk status at registration according to the International Metastatic RCC Database Consortium (IMDC) criteria (Appendix 5).

(f) NSCLC (Part 7B)

(i) Subjects with histologically confirmed Stage IV or recurrent NSCLC (per the 7th IASLC) squamous or nonsquamous histology, with no prior systemic anticancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease.

(ii) Prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least 6 months prior to enrollment.

(iii) Prior definitive chemoradiation for locally advanced disease is also permitted as long as the last administration of chemotherapy or radiotherapy (which ever was given last) occurred at least 6 months prior to enrollment.

(g) Bladder (Part 8)

(i) Histologically or cytologically confirmed urothelial carcinoma (including mixed histologies of urothelial carcinoma with elements of other subtypes) of the renal pelvis, ureter, bladder, or urethra with progression or refractory disease.

(ii) Subjects will need to have a pre-treatment and 2 on-treatment biopsies.

(iii) Prior therapy requirement:

Subjects must have been offered and/or have received or refused 1 prior platinum-based therapy for the treatment of metastatic or locally advanced unresectable disease. Subjects must have not received more than 1 prior systemic therapy. Reason(s) for refusal should be documented.

Subjects must be immunotherapy treatment naïve (eg, no prior therapy with experimental anti-tumor vaccines; any T-cell co-stimulation or checkpoint pathways, such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, including ipilimumab; or other medicines specifically targeting T-cells).

(iv) Within 12 months of peri-operative (neo-adjuvant or adjuvant) treatment with a platinum agent in the setting of cystectomy for localized muscle-invasive urothelial cancer.

(v) Sequential chemotherapy given as a planned sequence to optimize response will count as 1 regimen.

(vi) Vaccines for infectious disease (e.g., influenza) allowed, provided they are administered ≥ 2 weeks prior to or ≥ 2 weeks after study treatment/vaccine.

(h) TNBC and ER-Low Positive Breast Cancer (Part 9)

(i) **Not applicable per site-specific Protocol Amendment 04. See 2) (h) (vi).** Histologically confirmed breast cancer [per local laboratory, ER<1 (Allred score) by American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP), PR<1 (Allred score) by ASCO/CAP, and HER2-negative per current NCCN guidelines (www.nccn.org)].[179]

(ii) Subjects need to have 1 pre-treatment and 1 on-treatment biopsy. For the pre-treatment biopsy, archived material is acceptable if at least 2 tumor-bearing cores are available, and the material is obtained in the advanced/metastatic setting within 3 months of enrollment, with no intervening anti-neoplastic systemic therapies.

(iii) **Not applicable per site-specific Protocol Amendment 04. See 2) (h) (viii).** Stage IV metastatic or unresectable disease with zero or one prior systemic therapies in the advanced/metastatic setting. Subjects with < 12 months from receipt of last curative-intent chemotherapy are allowed; curative chemotherapy will be considered first-line therapy. Prior receipt of chemotherapy in the (neo)adjuvant setting is acceptable, as long as completed greater than 6 months from start of treatment.

(iv) **Not applicable per site-specific Protocol Amendment 04. See 2) (h) (x).** Vaccines for infectious disease (e.g., influenza) allowed, provided they are administered ≥ 2 weeks prior to or ≥ 2 weeks after study treatment/vaccine. Part 9 will allow the DRibbleDRibbles vaccine as part of subject treatment.

(v) **Not applicable per site-specific Protocol Amendment 04. See 2) (h) (ix).** Subjects must be immunotherapy treatment naïve (eg, no prior therapy with experimental anti-tumor vaccines; any T-cell co-stimulation or checkpoint pathways, such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, including ipilimumab; or other medicines specifically targeting T-cells). Prior receipt of intralymphatic cytokine therapy (IRX-2) is acceptable.

(vi) Histologically confirmed breast cancer [per local laboratory, ER < 1% expression by IHC staining for triple negative breast cancer and ER 1% through 10% for ER-low positive breast cancer by American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP), PgR < 1% for triple negative breast cancer by ASCO/CAP, and HER2-negative per current NCCN guidelines (www.nccn.org)].[180]

(vii) Prior endocrine therapy in ER-low positive participants is permitted.

(viii) Stage IV metastatic or unresectable disease with 0 through 2 prior chemotherapy-containing regimens in the advanced/metastatic setting of which no more than 1 prior line may include an anti-PD-1 or an anti-PD-L1 checkpoint inhibitor. Subjects with < 12 months from receipt of last curative-intent chemotherapy are allowed; curative chemotherapy will be considered first-line therapy. Prior receipt of chemotherapy in the (neo)adjuvant setting is acceptable, as long as completed greater than 6 months from start of treatment.

(ix) Anti-PD-1 or anti-PD-L1 antibody is permitted after a washout period of any time greater than 4 weeks from the last treatment.

(x) Approved or authorized vaccines for infectious disease (eg, influenza and SARS-CoV-2) are allowed, provided they are administered ≥ 10 days prior to or ≥ 10 days after study treatment/vaccine. Part 9 will allow the DRibbles (DPV-001) vaccine as part of subject treatment. Any vaccine(s) other than Fluzone® or the study vaccine DPV-001 must first be discussed with the BMS medical monitor.

3) Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1

4) Presence of at least 1 lesion with measurable disease as defined by RECIST v1.1 for response assessment. Subjects with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided the lesion(s) have demonstrated clear progression and can be measured accurately.

5) All subjects require a fresh tumor biopsy, these subjects must have at least one lesion accessible for pre- and on-treatment biopsy, in addition to the minimum one RECIST v1.1 measureable lesion required for response assessment. This lesion needs to be distinct from index lesion(s) being evaluated for radiological response.

6) Parts 1-7 subjects with prior exposure to therapy with any agent specifically targeting checkpoint pathway inhibition (such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-LAG-3, and anti-CTLA-4 antibody) are permitted after a washout period of any time greater than 4 weeks from the last treatment.

Note: *(i) Subjects who experienced prior Grade 1 to 2 checkpoint therapy-related immune-mediated AEs must have confirmed recovery from these events at the time of study entry,* ***other than endocrinopathies treated with supplementation****, as documented by resolution of all related clinical symptoms, abnormal findings on physical examination, and/or associated laboratory abnormalities. Where applicable, these subjects must also have completed steroid tapers for treatment of these AEs by a minimum of 14 days prior to commencing treatment with study therapy.*

(ii) Eligibility of subjects with prior ≥ Grade 3 checkpoint therapy-related immune AEs, will be considered on a case-by-case basis after discussion and agreement between the investigators and the medical monitor (eg, asymptomatic isolated Grade 3 lipase

elevations without clinical or radiological features of pancreatitis will be permitted to enroll).

7) Prior palliative radiotherapy must have been completed at least 2 weeks prior to first dose of study drug. Subjects with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of first dose of study drug are strongly encouraged to receive palliative radiotherapy prior to enrollment.

8) **All Subjects** must consent to the acquisition of pre- and on-treatment tumor biopsies for performance of correlative biomarker studies. Archival specimens may not be substituted for fresh baseline specimens (except for Part 9) but can be submitted to help understand the evolution of the tumor (ie, PD-L1 expression changes over time) for performance of correlative studies. Subjects who either do not consent to a pre-treatment tumor biopsy or do not have accessible lesions are not eligible. (However, subjects whose pre-treatment biopsy yields inadequate tissue quantity or quality will not be ineligible on this basis alone). For Part 9, please refer to above inclusion criteria.

9) **All Subjects enrolled** will be required to undergo mandatory pre- and on-treatment biopsies at acceptable clinical risk as judged by the investigator.

(a) The solid tumor tissue specimen must be a core needle, excisional, or incisional biopsy. Fine needle biopsies, drainage of pleural effusions with cytospins, or punch biopsies are not considered adequate for biomarker review. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable.

(b) Biopsied lesions should be distinct from index lesion(s) being evaluated for radiological response

10) Adequate organ function for subjects as defined by the following:

(a) Neutrophils ≥ 1500/μL

(b) Platelets ≥ 80×10^3/μL (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)

(c) Hemoglobin ≥ 8 g/dL (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)

(d) ALT and AST ≤ 3× upper limit of normal (ULN)

(e) Total bilirubin ≤ 1.5 × ULN (except subjects with Gilbert's Syndrome who must have normal direct bilirubin)

(f) Normal thyroid function or stable on hormone supplementation, per investigator assessment

(g) Albumin ≥ 2 g/dL

(h) Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CrCl) ≥ 40 mL/min (measured using the Cockcroft-Gault formula below):

Female CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{}$

$$\text{Male CrCl} = \frac{72 \times \text{serum creatinine in mg/dL}}{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00} \quad \frac{}{72 \times \text{serum creatinine in mg/dL}}$$

11) Ability to comply with treatment, PK, and PD sample collection and required study follow-up

Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (eg, subject has not been treated). If re-enrolled, the subject must be re-consented.

3) Age and Reproductive Status

a) Men and women, ages ≥ 18 years at the time of informed consent

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotrophin [hCG]) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding

d) For Parts 1-8, WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug BMS-986178 plus 5 half-lives of study drug plus 30 days as defined below. This duration should be 12 weeks for Parts 1 and 3 subjects (50 days plus 30 days) or 5 months for Part 2 subjects (130 days plus 30 days [duration of ovulatory cycle]), for a total of up to 160 days post-treatment completion. For Part 9, WOCBP must agree to follow instructions for method(s) of contraception for duration of study therapy plus 1 year after last dose of study therapy as defined below.

e) For Parts 1-8, males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug BMS-986178 plus 5 half-lives of the study drug plus 90 days. The duration should be 20 weeks for Parts 1 and 3 subjects (50 days plus 90 days) or 7 months for Part 2 subjects (130 days plus 90 days [duration of sperm turnover]), for a total of up to 220 days post-treatment completion. For Part 9, males who are sexually active must agree to follow instructions for method(s) of contraception for the duration of treatment plus 4 months after the last dose of study therapy. For Parts 1-9, male subjects must be willing to refrain from sperm donation during this time.

f) For Parts 1-8, azoospermic males are exempt from contraceptive requirements. For Part 9, azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participant has undergone a successful vasectomy or if the partner is pregnant. For Parts 1-9, WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, but must still undergo pregnancy testing as described in this section.

Investigators shall counsel women of child bearing potential (WOCBP) and male participants (as defined below), who are sexually active with WOCBP, on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study intervention, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP must use a highly effective method of contraception (listed below). WOCBP partners of male subjects must use a highly effective method of contraception. Local laws and regulations may require use of alternative and/or additional contraception methods. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Male subjects are expected to use a condom, in addition to a highly effective method as noted in the list below:

1) Progestogen only hormonal contraception associated with inhibition of ovulation
2) Hormonal methods of contraception including oral contraceptive pills containing combined estrogen and progesterone, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena®
3) Nonhormonal IUDs, such as ParaGard®
4) Bilateral tubal occlusion
5) Vasectomized partner with documented azoospermia 90 days after procedure
    - Vasectomy is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
6) Intrauterine hormone-releasing system
7) Complete abstinence
    - Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms)
    - Complete abstinence is an acceptable form of contraception for all study drugs and must be used at least 30 days prior to first dose of study drug and throughout the duration of the study treatment (plus 5 half-lives of the study drug(s) plus 30 days).
    - It is not necessary to use any other method of contraception when complete abstinence is elected.
    - Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 5.1.
    - Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
    - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
8) Use a condom in male subjects with female partners.

UNACCEPTABLE METHODS OF CONTRACEPTION

1) Periodic abstinence (calendar, symptothermal, and/or post-ovulation methods)
2) Withdrawal (coitus interruptus)
3) Spermicide only
4) Lactation amenorrhea method
5) Diaphragm with spermicide
6) Cervical cap with spermicide
7) Vaginal sponge with spermicide
8) Male or female condom with or without spermicide*
9) Progestogen-only oral hormonal contraception by WOCBP, where inhibition of ovulation is not the primary mode of action or male subject's WOCBP partner

* A male and a female condom must not be used together.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Subjects with known or suspected CNS metastases or untreated CNS metastases, or with the CNS as the only site of disease, are excluded. However, subjects with controlled brain metastases will be allowed to enroll. For Parts 1-8, controlled brain metastases are defined as no radiographic progression for at least 4 weeks following radiation and/or surgical treatment (or 4 weeks of observation if no intervention is clinically indicated), and off of steroids for at least 2 weeks, and no new or progressive neurological signs and symptoms. For Part 9 only, participants are eligible if CNS metastases have been treated and participants have neurologically returned to baseline (except for residual signs or symptoms related to CNS treatment). In addition, participants must have been either off corticosteroids for at least 2 weeks prior to randomization. Imaging performed within 28 days prior to randomization must document radiographic stability of CNS lesions and be performed after completion of any CNS-directed therapy.

b) Subjects with carcinomatous meningitis

c) For ovarian cancer (Part 3B):

i) Ovarian cancer subjects with history of bowel obstruction in the prior 6 months or with intraperitoneal catheter (eg Tenckhoff) will be excluded.

ii) Not applicable

d) For NSCLC (Part 7B)

i) Subjects with known EGFR mutations, which are sensitive to available targeted inhibitor therapy (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution mutations), are excluded. All subjects with non-squamous histology must have been tested for EGFR mutation status; use of an

FDA-approved test is strongly encouraged. Subjects with non-squamous histology and unknown or indeterminate EGFR status are excluded.

ii) Subjects with known ALK translocations, which are sensitive to available targeted inhibitor therapy, are excluded. If tested, the use of an FDA-approved test is strongly encouraged. Subjects with unknown or indeterminate ALK status may be enrolled.

e) For Bladder Cancer (Part 8)

i) Prior therapy with experimental anti-tumor vaccines, any T-cell co-stimulation or checkpoint pathways, such as anti-PD1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, including ipilimumab, or other medicines specifically targeting T-cells is also prohibited in this part of the study.

ii) No prior adverse reaction to tetanus toxoid-containing vaccines.

iii) Subjects with known allergies to egg products, neomycin, or tetanus toxoid are also considered ineligible.

f) For TNBC and ER-Low Positive Breast Cancer (Part 9)

i) **Not applicable per site-specific Protocol Amendment 04. See f) ii).** Prior treatment with experimental anti-tumor vaccines; any T-cell co-stimulation or checkpoint pathways, such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, including ipilimumab; or other medicines specifically targeting T-cells. Prior receipt of intralymphatic cytokine therapy (IRX-2) is acceptable.

ii) Prior treatment with experimental anti-tumor vaccines; any T-cell co-stimulation or checkpoint pathways (other than anti-PD-1/anti-PD-L1), such as anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, including ipilimumab; or other medicines specifically targeting T-cells. Prior receipt of intralymphatic cytokine therapy (IRX-2) and anti-PD-1/anti-PD-L1 antibody is acceptable.

2) Medical History and Concurrent Diseases

a) Subjects with a prior malignancy, different from the one used for enrollment in this study, diagnosed within less than 2 years prior to study entry are excluded (except non-melanoma skin cancers and in situ cancers such as bladder, colon, cervical/dysplasia, melanoma, or breast). In addition, subjects with other second malignancies diagnosed more than 2 years ago who have received therapy with curative intent with no evidence of disease during the interval who are considered by the investigator to present a low risk for recurrence will be eligible.

b) Subjects with other active malignancy requiring concurrent intervention are excluded.

c) Prior organ allograft

d) Previous treatment:

i) Prior anti-cancer treatments are permitted (ie, chemotherapy, radiotherapy, hormonal, or immunotherapy) except in Parts 6B (Inclusion criteria 1.a)(1)2)(e)) and 7B (Inclusion criteria 1.a)(1)2)(f)).

ii) Toxicity (except for alopecia) related to prior anti-cancer therapy and/or surgery must either have resolved, returned to baseline or Grade 1, or have been deemed irreversible.

iii) For cytotoxic agents, at least 4 weeks or 5 half-lives (whichever is shorter) must have elapsed between the last dose of prior anti-cancer therapy and initiation of study therapy.

iv) For non-cytotoxic agents, at least 4 weeks or 5 half-lives (whichever is shorter) must have elapsed from last dose of prior anti-cancer therapy and the initiation of study therapy. If 5 half-lives is shorter than 4 weeks, agreement with Sponsor/medical monitor is mandatory.

e) Subjects with prior therapy with any agent specifically targeting T-cell co-stimulation pathways such as anti-OX40 antibody, anti-CD137, anti-GITR antibody, and anti-CD27 are excluded.

f) Subjects with active, known, or suspected autoimmune disease are excluded. Subjects with vitiligo, type 1 diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, euthyroid subjects with a history of Grave's disease (subjects with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin prior to first dose of study drug), psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. Subjects with well controlled asthma and/or mild allergic rhinitis (seasonal allergies) are eligible.

g) Subjects with history of life-threatening toxicity related to prior immune therapy (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after adrenal crisis)

h) Subjects with interstitial lung disease that is symptomatic or that may interfere with the detection or management of suspected drug-related pulmonary toxicity

i) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration except for adrenal replacement steroid doses > 10 mg daily prednisone equivalent in the absence of active autoimmune disease. **Note**: Treatment with a short course of steroids (< 5 days) up to 7 days prior to initiating study drug is permitted.

j) Uncontrolled or significant cardiovascular disease, including but not limited to any of the following:

i) Myocardial infarction or stroke/transient ischemic attack within the past 6 months

ii) Uncontrolled angina within the past 3 months

iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)

iv) History of other clinically significant heart disease (eg, cardiomyopathy, myocarditis, congestive heart failure with New York Heart Association functional classification III-IV, pericarditis, significant pericardial effusion)

v) Cardiovascular disease-related requirement for daily supplemental oxygen therapy

vi) QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation > 480 msec

k) History of any chronic hepatitis as evidenced by the following:

i) Positive test for hepatitis B surface antigen

ii) Positive test for qualitative hepatitis C viral load (by polymerase chain reaction [PCR])

Note: Subjects with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible. History of resolved hepatitis A virus infection is not an exclusion criterion.

Additional testing or substitute testing per institutional guidelines to rule out infection is permitted.

l) Evidence of active infection that requires systemic antibacterial, antiviral, or antifungal therapy ≤ 7 days prior to initiation of study drug therapy (does not apply to viral infections that are presumed to be associated with the underlying tumor type required for study entry).

m) Known history of testing positive for HIV or known acquired immunodeficiency syndrome. **Note:** Testing for HIV must be performed at sites where mandated by local requirements.

n) **Not applicable per site-specific Protocol Amendment 04. See 2) r).** Any major surgery within 4 weeks of study drug administration. Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study drug.

o) Use of non-oncology vaccines containing live/attenuated virus for prevention of infectious diseases within 4 weeks prior to study drug. The use of inactivated seasonal influenza vaccines, eg, Fluzone®, will be permitted on study without restriction, however, for subjects treated in Part 9, any vaccine (including inactivated) must first be discussed with the BMS medical monitor. Previous SARS-CoV-2 vaccines less than 10 days prior to start of study drug. For vaccines requiring more than 1 dose, the full series (eg, both doses of a 2-dose series) should be completed prior to start of study treatment when feasible and when a delay in enrollment would not put the study subject at risk.

p) Use of packed red blood cell or platelet transfusion within 2 weeks prior to the first dose of study drug

q) A known or underlying medical or psychiatric condition and/or social reason that, in the opinion of the investigator or Sponsor, could make the administration of

study drug hazardous to the subject or could adversely affect the ability of the subject to comply with or tolerate the study.

r) Any major surgery within 2 weeks of study drug administration. Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days and have adequate wound healing before the first dose of study drug.

s) Participant has any condition, including active or uncontrolled infection, or the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study. Previous SARS-CoV-2 infection within 10 days for mild or asymptomatic infections or 20 days for severe/critical illness prior to first dose of study drug. Acute symptoms must have resolved and based on investigator assessment in consultation with the medical monitor, there are no sequelae that would place the participant at a higher risk of receiving study treatment.

t) Subjects who are pregnant and/or breastfeeding.

3) Allergies and Adverse Drug Reaction

a) History of allergy to nivolumab or ipilimumab (Parts 2, 4, and 9 or 3 and 5, respectively) or history of allergy to the combination of nivolumab and ipilimumab (Parts 6 and 7)

b) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity) to prior anti-cancer immune modulating therapies (eg, checkpoint inhibitors, T-cell co-stimulatory antibodies)

4) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances, a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply, and BMS approval is required.)

b) Subjects who are compulsorily detained for the treatment of either psychiatric or physical (eg, infectious disease) illness

c) Inability to comply with restrictions and prohibited activities/treatments as listed in Section 3.4

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must

have a documented serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The durations of the washout period in the following are suggested guidelines, and investigators should use their judgment in checking serum FSH levels:

- 1 week minimum for vaginal hormonal products (eg, rings, creams, and gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

[redacted]

[redacted]

3.5 Discontinuation of Subjects Following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment and/or participation in the study
- Any clinical AE, laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either psychiatric or physical (eg, infectious disease) illness
- Pregnancy

- Documented disease progression as defined by RECIST (see Appendix 3) unless the subject meets the criteria for treatment beyond progression (Section 3.5.1)
- Clinical deterioration while receiving active study therapy that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Inability to comply with protocol requirements
- Discretion of the investigator
- Protocol-defined reasons for discontinuation (see Section 4.5.6)

In case of pregnancy, the investigator must immediately notify the BMS medical monitor/designee of this event. In the event that a female subject becomes pregnant during a clinical trial, the study drug must be discontinued immediately. Please call the BMS medical monitor within 24 hours of awareness of the pregnancy (Section 6.4).

All subjects who discontinue the investigational product should comply with the protocol-specified follow-up procedures outlined in Table 5.1-9. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of a psychiatric or physical illness).

If the study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate CRF page.

3.5.1 Treatment Beyond Disease Progression

As described in Section 1.1.20 accumulating evidence indicates that a minority of subjects with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease. Subjects will be permitted to continue on treatment beyond initial RECIST v1.1 (see Appendix 3)-defined progressive disease as long as they meet the following criteria:

- Investigator-assessed clinical benefit and without rapid disease progression
- Continue to meet all other study protocol eligibility criteria
- Subject tolerates study drug
- Subject has stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases).
- Subject provides written informed consent prior to receiving any additional BMS-986178, nivolumab, and/or ipilimumab treatment using an ICF describing any reasonably foreseeable risks or discomforts or other alternative treatment options.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. As described in Section 3.1.8, all decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor, and an assessment of the risk/benefit of continuing with study therapy must be documented in the study records. Subjects will be re-consented to explain the rationale for this ongoing treatment.

3.5.1.1 Discontinuation due to Further Progression

Subjects should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from the time of initial progression (including all target lesions and new measurable lesions).

The tumor burden volume from the time of initial progression should be used as the reference baseline for comparison with the postprogression assessment.

Any new lesion considered non-measurable at the time of initial progression may become measurable, and therefore, must be included in the tumor burden measurement as follows:

For solid tumors: New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm).

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond the initial investigator-assessed, RECIST v1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

3.5.1.2 Assessment Schedule for Subjects with Post-progression Treatment

Subjects should continue to receive monitoring according to the on-treatment assessments in Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, Table 5.1-6, Table 5.1-8, and Table 5.1-9. Radiographic assessment by computed tomography (CT) (preferred) or MRI described in Section 5.1 and Appendix 3 is required when subjects continue post-progression treatment. For subjects that discontinue postprogression treatment with study therapy, no additional radiographic assessments will be required.

3.6 Post-study Drug Follow-up

Post-study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed per the Safety Follow-up (approximately 100 days).

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The

withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes, texts, or emails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If the investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

In this study, all drugs will be considered investigational products: BMS-986178, nivolumab, ipilimumab, tetanus vaccine, and UbiLT3 and UbiLT6 (Table 4-1).

Product description and storage information are described in Table 4-1.

Table 4-1: Study Drugs for CA012004

Product Description Class and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per label)
BMS-986178 Injection	25 mg/mL (80 mg/vial)	IP	Open Label	Vial	Store at 2°C to 8°C; do not freeze; protected from light.
Nivolumab Injection	10 mg/mL (100 mg/vial)	IP	Open Label	Vial	Store at 2°C to 8°C; store in original package; do not freeze; protected from light.

Table 4-1: Study Drugs for CA012004

Product Description Class and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per label)
Ipilimumab Injection	5 mg/mL (200 mg/vial)	IP	Open Label	Vial	Store at 2°C to 8°C; do not freeze; protected from light.
Tetanus vaccine	Per local[a]	IP	Open Label	Various packaging configurations	Refer to the label on container and/or package insert
UbiLT3 and UbiLT6 vaccine[b]	1 mg/mL and as per Pharmacy Manual	IP	Open Label	Vial and various packaging configurations	Refer to label on container and/or package insert or pharmacy manual.

Abbreviations: IB = Investigator Brochure; IP = investigational product

[a] Tetanus vaccine (Tdap preferred, Td or equivalent after discussion with the medical monitor) will be obtained as local commercial product in countries if allowed by local regulations or through investigating sites standard prescribing procedures.

[b] DPV-001 (UbiLT3 and UbiLT6) will be provided by Ubivac.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that the investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, the investigational products are BMS-986178, nivolumab, ipilimumab, UbiLT3 and UbiLT6, and tetanus vaccine.

4.2 Non-Investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the SOC for a given diagnosis, may be considered as non-investigational products.

Cyclophosphamide is a non-investigational product(s) in this protocol. BMS will not supply, as cyclophosphamide will be sourced locally by sites through investigating sites standard prescribing procedures.

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets). Please refer to Section 9.2.2 for guidance on IP records and documentation.

BMS-986178 Preparation

Calculated dosages for solutions for infusion may be mixed in a D5W bag or normal saline (0.9% NaCl) bag to a recommended concentration. Further details with regard to specific concentrations for drug dilution and administration will be provided in the pharmacy dosing manual for BMS-986178.

BMS-986178 Administration

The administration of the entire bag or syringe (if syringe pump is used) contents should be infused over approximately 30 minutes (including a flush up to 20 mL to completely flush the infusion line), through an IV infusion set (sterile, non-pyrogenic diethylhexyl phthalate [DEHP]-free and non-DEHP free components, low protein binding, polyethersulfone or nylon 0.2-µm in line filter, which will be supplied by the site). Care must be taken to ensure the sterility of the prepared solution, as the drug product does not contain antimicrobial preservatives or bacteriostatic agents. Equilibration to room temperature is recommended for the drug product, infusion fluid, and their combination prior to administration.

Diluted solutions of BMS-986178 for injection are stable for up to 24 hours, at either refrigerated conditions, 2° to 8°C (36° to 46°F), and light protected; 4 hours of which can be under ambient temperature 15 to 25°C (59° to 77°F), and ambient light conditions. The diluted bag should not be shaken. Infusion of BMS-986178 injection must be completed within 24 hours of dilution. The start of drug infusion equals zero (0) hour.

For treatment visits in which both BMS-986178 and nivolumab are administered, nivolumab will be administered first followed by BMS-986178 after a minimum of 30 minutes following completion of the nivolumab infusion and flush. Further details regarding preparation and administration will be provided separately in site/pharmacy training materials and Investigator's Brochure for BMS-986178.[170]

For treatment visits in which both BMS-986178 and ipilimumab are administered, ipilimumab will be administered first followed by BMS-986178 after a minimum of 30 minutes following completion of the ipilimumab infusion and flush. Further details regarding preparation and administration will be provided separately in site/pharmacy training materials and Investigator's Brochure for BMS-986178.[170]

For treatment visits in which BMS-986178, nivolumab, and ipilimumab are administered, nivolumab will be administered first followed by ipilimumab then BMS-986178. After each 30-minute infusion, there will be a 30-minute waiting period and a flush before starting the next study drug infusion. Further details regarding preparation and administration will be provided separately in site/pharmacy manual and Investigator's Brochure for BMS-986178.[170]

DRibbles Vaccine Preparation

DPV-001 Storage and Handling

UbiLT3 and UbiLT6 DRibble vaccine is shipped under liquid nitrogen conditions and stored frozen at -60 ºC to -90 ºC.

The vaccine consists of a cellular product that is enriched for autophagosomes from the UbiLT3 and UbiLT6 cell lines and is cryopreserved in hetastarch. Packaging consists of a 1.5 mL cryovial.

DPV-001 Preparation

The vial of UbiLT3 and/or UbiLT6 will be thawed in a 37ºC (± 2ºC) water bath, vortexed, loaded into a syringe, kept on ice and administered within 4 hours of thawing (refer to pharmacy manual for additional information). DPV-001 for injection should be withdrawn from vials by syringe to required volume, 1 mg flat dose (0.5 mg each when both UbiLT3 and UbiLT6 are given). Vaccine may be given as multiple injections due to volume, according to institutional policy.

Further details with regard to specific drug dispensing and administration will be provided in the package insert, pharmacy manual, or DPV-001 IB.[53]

DPV-001 Administration

The first vaccination of UbiLT3 and UbiLT6 (components of DPV-001) is administered IN under ultrasound guidance.

The second vaccination of UbiLT3 and UbiLT6 is administered ID on C1D8.

On C1D15, the subjects will receive DPV-001 followed by nivolumab. DPV-001 will consist of only UbiLT3 1 mg ID. After the administration of UbiLT3, the subject will be administered nivolumab at 240 mg infusion over 30 minutes. Alternating of DPV-001 vaccine components is a heterologous prime-boost strategy.

Starting at cycle 2, nivolumab will be given on day1 of each cycle as a 480 mg flat dose (q4w) infusion over 30 minutes. DPV-001 1 mg ID will alternate between either UbiLT3 or UbiLT6. UbiLT6 will be given on C2D1, C3D1, C5D1, and C9D1. UbiLT3 1 mg ID will be given on C2D15, C4D1, C6D1, and C12D1.

For treatment with DPV-001, nivolumab, with or without BMS-986178, there will be a waiting period after DPV-001 administration of 60 minutes on C1D1 and 30 minutes for all subsequent doses. After the waiting period, nivolumab will then be infused over 30 minutes, followed by a 30 minutes waiting period before BMS-986178 can be given. DPV-001 will be administered intranodally under ultrasound guidance on C1D1, then intradermally on C1D8 and beyond. Further details regarding preparation and administration will be provided separately in site/pharmacy manual and Investigator's Brochure for DPV-001.[53]

Cyclophosphamide Administration

Commercial cyclophosphamide will be sourced locally per site prescribing procedures and administered IV at 300 mg/m^2 over a 30 to 60 minute infusion on day -3.

4.4 Method of Assigning Subject Identification

This is an open-label study. All enrolled subjects, including those not dosed, will be assigned sequential subject numbers starting with 00001, (eg, 00001, 00002, 00003... 00010). Those enrolled subjects meeting the inclusion and exclusion criteria will be eligible to be dosed.

Once informed consent has been obtained, the investigator (or designee) will register the subject by an IRT.

The following information is required for registration:

- Gender
- Diagnosis (if applicable)
- Statement that subject is eligible
- Date of informed consent
- Date of Birth

Based on the rate of subject enrollment, the Sponsor will implement an IRT to assign subject numbers, study part and dose level as well as manage drug supply. IRT instructions will be provided to the sites in a separate instruction manual.

Treatment group/dose level will be provided to the site study team through the IRT after the subject has been deemed eligible and is assigned for the study. Site personnel/investigator will receive a receipt confirming the treatment assignment. A copy of this documentation should remain in the subject's chart. Because of the nature of the study design, limited early access to the assignment information will be granted to the study team.

Once it is determined that the subject meets the eligibility criteria, the investigative site will register the subject through IRT prior to the first study drug administration.

Subjects will be assigned to a part or a cohort within a part by IRT. Details about how the subjects will be assigned to a specific part/cohort will be provided in IRT training documentation.

In the dose escalation phases, if a subject discontinues treatment with either BMS-986178, nivolumab, or ipilimumab during the DLT period for reasons other than a DLT, the subject may be replaced with a new subject, if necessary, for safety assessments. Replacement subjects will receive the same treatment but will be assigned a new subject number.

Additional subjects may be added to expansion cohorts and Part 8 if adequate paired pre-treatment and on-treatment biopsy specimens are not obtained from previously assigned subjects. The additional subjects will receive the same treatment as the subjects being replaced, but new subject numbers will be assigned.

Subjects may be permitted to rescreen for the study following agreement between the investigator and the Sponsor/medical monitor.

Part 9

All Part 9 participants will be randomized in a 2:1 ratio to receive either combination of BMS-986178, nivolumab, DPV-001 vaccine, single dose cyclophosphamide (cohort 1) or combination of nivolumab, DPV-001 vaccine, and single dose cyclophosphamide (cohort 2).

4.5 Selection and Timing of Dose for Each Subject

Each subject will be assigned to a specific dose level as listed in Section 4.4 during dose escalation. Subjects in the dose expansion will be treated at the MTD, or at the RP2D, as agreed upon by the investigators and the Sponsor.

Nivolumab will be administered as flat doses. There will be no dose escalations or reductions of nivolumab allowed once assigned. There are no premedications recommended for nivolumab on the first cycle. If an acute infusion reaction is noted, the subjects should be managed according to Section 4.5.7.

Ipilimumab will be administered at 1 or 3 mg/kg. There will be no dose escalations or reductions of ipilimumab allowed once assigned. There are no premedications recommended for ipilimumab on the first cycle. If an acute infusion reaction is noted, the subjects should be managed according to Section 4.5.7.

There will be no dose escalations or reductions of DPV-001 allowed once assigned.

There will be no dose escalations or reductions of BMS-986178 allowed once assigned.

4.5.1 Dose Limiting Toxicity

For the purpose of guiding dose escalation, DLTs will be defined based on the incidence, severity, and duration of AEs, for which no clear alternative cause is identified and that occur within 28 days of initiation of study drug(s). AEs will be graded according to the NCI CTCAE v4.03.

For the purpose of subject management, potential DLTs that occur at any time, whether during dose escalation or dose expansion, will result in all study drug(s) being held pending evaluation of the event's relatedness to study drug, severity, duration, and in accordance with Section 4.5.4. Subjects must meet criteria for treatment prior to re-initiation of study treatment (see Section 4.5.5).

For the purpose of subject management, an AE that meets the DLT criteria, regardless of the cycle in which it occurs, will lead to discontinuation of study drug(s) except for exceptions as outlined in Section 4.5.6. Such subjects will not be retreated with study drug(s) and will enter the Safety Follow-up period of the study.

Subjects who withdraw from the study during the DLT evaluation interval for reasons other than a DLT may be replaced with a new subject at the same dose level. The incidence of DLT(s) during the DLT evaluation period will be used in dose escalation decisions and to define the MTD. All AEs for which no clear alternative cause is identified occurring after the 28-day DLT period may be considered to represent DLTs for the purposes of defining the RP2D upon agreement between the Sponsor, medical monitor, and investigators, if they are determined to have no clear alternative cause and not related to disease progression. DLT criteria will be utilized for the evaluation of a manageable and tolerable dose in the schedule and dose exploration parts (Parts 4, 5, and 8) and safety cohorts (Parts 6A and 7A).

Any one of the following events for which an alternative cause cannot be identified will be considered a DLT:

A. Hepatic DLT

- Any ≥ Grade 3 elevation of AST, ALT, or total bilirubin
- Grade 2 AST or ALT with symptomatic liver inflammation (eg, right upper quadrant tenderness, jaundice, pruritus)
- AST or ALT > 3 × ULN and concurrent total bilirubin > 2 × ULN without initial findings of cholestasis (elevated serum alkaline phosphatase (eg, findings consistent with Hy's law or FDA definition of potential drug-induced liver injury [pDILI]) (Note that this special category of DLT uses ULN rather than CTC Grade for definition.)

B. Non-hepatic DLT

- Grade 2 or greater uveitis, episcleritis, or iritis
- Any other Grade 2 eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment
- Grade 3 or greater pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction
- Any Grade 3 or greater non-dermatologic, non-hepatic toxicity will be considered a DLT with the following specific EXCEPTIONS:
    - ♦ Grade 3 or Grade 4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 72 hours, and either resolve spontaneously or respond to conventional medical intervention
    - ♦ Grade 3 nausea, vomiting, or diarrhea that lasts less than 72 hours, and either resolves spontaneously or responds to conventional medical intervention
    - ♦ Grade 3 or 4 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
    - ♦ Isolated Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical, or laboratory evidence of impaired end-organ perfusion)

- ♦ Grade 3 endocrinopathy that is well controlled by hormone replacement
- ♦ Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor)
- ♦ Grade 3 fatigue for ≤ 7 days
- ♦ Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours

C. Dermatologic DLT

- Grade 4 rash
- Grade 3 rash if no improvement (ie, resolution to ≤ Grade 1) after a 1- to 2-week infusion delay. Subjects who have not experienced a Grade 3 skin AE may resume treatment in the presence of Grade 2 skin toxicity.

D. Hematologic DLT

- Grade 4 neutropenia ≥ 7 days in duration
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with clinically significant bleeding, or any requirement for platelet transfusion
- Grade 4 anemia not explained by underlying disease
- Grade ≥ 3 febrile neutropenia
- ≥ Grade 3 hemolysis (ie, requiring transfusion or medical intervention such as steroids)

4.5.2 Management Algorithms for Immuno-Oncology Agents

IO agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab, ipilimumab, and BMS-986178 are considered IO agents in this protocol. Early recognition and management of AEs associated with IO agents may mitigate severe toxicity. Management algorithms in Appendix 2 have been developed from extensive experience with nivolumab and ipilimumab to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological
- Myocarditis
- The clinical nature of AEs noted with BMS-986178 will determine the role of the above algorithms for use in toxicities related to its use in this study.

The algorithms recommended for utilization in this protocol are included in Appendix 2.

4.5.3 Guidelines for Dose Modification

Intra-subject dose escalation or reduction of BMS-986178, nivolumab, ipilimumab, or DPV-001 is not permitted in this study in order to allow better evaluation of the extended safety and efficacy at individual dose levels and schedules.

4.5.4 Dose Delays due to Toxicity

Subjects who experience the following must have all study drug(s) held:

- Potential DLTs, until DLT relatedness is defined.
- Select AEs and laboratory abnormalities:
  - ≥ Grade 1 pneumonitis
  - ≥ Grade 2 abnormality in AST, ALT, total bilirubin
  - ≥ Grade 2 creatinine
  - ≥ Grade 2 non-skin, drug related AE, with the exception of fatigue
  - ≥ Grade 2 diarrhea or colitis
  - ≥ Grade 2 neurological AE
  - Grade 2 myocarditis
  - Grade 4 amylase and/or lipase abnormalities regardless of symptoms or clinical manifestation. (Grade 3 amylase or lipase increase that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay)
- AE, laboratory abnormality, or concurrent illness that, in the judgment of the Investigator, warrants delaying the dose of study drug.
- Confirmed SARS-CoV-2 infection.

If a dose delay is necessary for subjects who are receiving study treatment, all study drugs must be held. Dosing visits are to be delayed but not skipped to ensure that subjects will receive all scheduled treatment cycles if toxicity allows. During treatment, dosing will be as follows:

- Part 2 subjects will receive 12 doses (12 cycles) of q2w BMS-986178 and nivolumab combination therapy.
- Parts 3 and 5 subjects will receive up to 4 doses of q3w BMS-986178 and ipilimumab combination therapy and 4 doses of q3w BMS-986178 monotherapy during maintenance.
- Part 4 subjects will receive 6 doses (6 cycles) of q4w BMS-986178 and nivolumab combination therapy.
- Part 6 subjects will receive 4 doses of q3w BMS-986178, nivolumab, and ipilimumab combination therapy and 3 doses of q4w BMS-986178 and nivolumab during maintenance.
- Part 7 subjects will receive 4 cycles (1 cycle = 6 weeks) of q2w BMS-986178 and nivolumab and q6w ipilimumab combination therapy.
- Part 8
  - Cohorts 1-3 subjects will receive 9 doses of BMS-986178 (q12w) and 27 doses of nivolumab (q4w) combination therapy.

  - Cohort 4 subjects will receive 27 doses of nivolumab (q4w) monotherapy.
- Part 9
  - Cohort 1 subjects will receive 8 doses of BMS-986178 on Day 1 of Cycle 1-6, Cycle 9, and Cycle 12; 26 doses of nivolumab (Cycle 1 flat dose, q4w starting at Cycle 2); 11 doses of DPV-001 (UbiLT3 and/or UbiLT6), and a single dose of cyclophosphamide.
  - Cohort 2 subjects will receive 26 doses of nivolumab (Cycle 1 flat dose, q4w starting at Cycle 2); 11 doses of DPV-001 (UbiLT3 and/or UbiLT6), and a single dose of cyclophosphamide.

Subjects receiving BMS-986178 in combination with nivolumab, nivolumab and ipilimumab, or nivolumab and DPV-001 who have study treatment-related toxicities that meet the criteria for a dose delay should have all study drugs held until the criteria to resume treatment are met (see Section 4.5.5). Subjects who require a dose delay should be re-evaluated weekly, or more frequently if clinically indicated, and resume treatment when criteria are met. Continue tumor assessments per protocol even if dosing is delayed. Because nivolumab-, ipilimumab- and/or BMS-986178-related AEs require early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, gastrointestinal toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity, and renal toxicity (algorithms are provided in Appendix 2).

For subjects who have dose delays in Parts 1-7, the total study treatment period should not exceed 36 weeks, unless approved by the BMS Medical Monitor (or designee). Parts 8 and 9 will have a treatment period up to a maximum of 24 months of dosing from first dose regardless of treatment delays. Extensions to the period of dose delays may be granted for individual subjects on a case by case basis after specific consultation and agreement between the investigator and BMS medical monitor in settings where risk/benefit may justify continued study therapy (eg, subject deriving clinical benefit who requires prolonged steroid taper for the management of non-DLT drug-related AEs, or experiences delays for the management of a non-drug-related AE).

The end of cycle tumor assessments (ie, CT/MRI, etc) will continue every 8 weeks Parts 1-7 and 9 or every 12 weeks Part 8 (± 1 week) relative to the subject's first dose of BMS-986178, regardless of any treatment delay incurred.

4.5.5 Criteria to Resume Treatment

4.5.5.1 Criteria to Resume Treatment in Subjects with a Dose Delay

If a dose delay is necessary for subjects who are receiving study treatment, all study drugs must be held.

Subsequent dosing with study therapy may resume once non-DLT AEs resolve to Grade 1 or baseline.

Subjects experiencing AEs not meeting the criteria for permanent discontinuation as outlined in Section 4.5.6 may resume treatment with study medication under the following criteria:

- Subjects may resume treatment with study drug when the AE(s) resolve to Grade ≤ 1 or baseline value with the following exceptions:
  - Subjects may resume treatment in the presence of Grade 2 fatigue.
  - Subjects who have not experienced a Grade 3 skin AE may resume treatment in the presence of Grade 2 skin toxicity.
  - Subjects with Grade 2 eye pain or blurred vision not meeting DLT criteria (Section 4.5.1) must resolve to baseline prior to resuming study therapy.
  - Any pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for resumption of treatment if discussed with and approved by BMS Medical Monitor (or designee).
  - Subjects with endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor (or designee). Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - For subjects with Grade 2 AST, ALT and/or total bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
  - Subjects with a Grade 4 amylase or lipase increase that is not associated with symptoms or clinical manifestations of pancreatitis can be restarted on therapy once the levels have decreased to Grade 3 or lesser - and after consultation with the BMS Medical Monitor.
- If study treatment is delayed past the scheduled dosing visit per protocol, the scheduled study treatment administration will be delayed, but not skipped, until dosing resumes to ensure that subjects will receive all scheduled treatment cycles if toxicity allows.
- The consideration to re-initiate study therapy under these exceptions will be made on a case by case basis after considering the overall risk/benefit profile and in consultation between the investigator and the study Sponsor. Any AE with clinical risk will be assessed on a case by case basis with the investigator and the BMS Medical Monitor to determine the risks and benefits of continuing on therapy following resolution versus discontinuing therapy permanently. Continue tumor assessments per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies per protocol or more frequently if clinically indicated during such dosing delays.
- If dosing is delayed ≥ 9 weeks, the subject must be permanently discontinued from study treatment, except as specified in Section 4.5.6. Extensions to the period of dose delays may be granted for individual subjects on a case by case basis after specific consultation and agreement between the investigator and BMS medical monitor in settings where risk/benefit may justify continued study therapy (eg, subject deriving clinical benefit who requires prolonged steroid taper for the management of non-DLT immune-related AEs, or experiences delays for management of a non-drug-related AE).
- Dosing delays to allow prolonged steroid tapers to manage AEs are allowed. Additionally, dosing delays ≥ 9 weeks (as noted above) that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor.

- If the toxicity resolves to ≤ Grade 1 or baseline > 9 weeks after the last dose, the subject does not meet the criteria for permanent discontinuation (see Section 4.5.6), and the investigator believes that the subject is deriving clinical benefit, the subject may be eligible to resume study treatment(s) following approval from the BMS Medical Monitor (or designee).
- Tumor assessments should continue as per protocol even if dosing is delayed.
- Participants with confirmed SARS-CoV-2 infection may resume treatment after 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared, positive RT-PCR test result, or positive viral antigen test result, 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications), 3) evaluation by the investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, and 4) consultation by the medical monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled out and other criteria to resume treatment are met.
- Prior to re-initiating on-study treatment in a subject with a dosing delay due to SARS-CoV-2 infection, the medical monitor must be consulted.

4.5.5.2 Criteria for Resuming Treatment in Subjects with an Infusion Reaction

In subjects experiencing an infusion reaction with study drug administration, the following guidelines for dose delay and criteria to resume treatment are to be followed:

- Parts 2, 4, 6, 7, 8, and 9 on days with administration of BMS-986178 and nivolumab only: If a nivolumab-related infusion reaction prevents subsequent infusion of BMS-986178 on the same day, the dose of BMS-986178 should be replaced as soon as possible. In such instances, at least 12 days must elapse between the replacement dose of BMS-986178 and the administration of the next dose of nivolumab combined with BMS-986178.
- Parts 3 and 5: If an ipilimumab-related infusion reaction prevents subsequent infusion of BMS-986178 on the same day, the dose of BMS-986178 should be replaced as soon as possible. In such instances, at least 19 days must elapse between the replacement dose of BMS-986178 and the administration of the next dose of ipilimumab combined with BMS-986178 on a q3w schedule.
- Parts 6 or 7: If a nivolumab-related infusion reaction prevents subsequent infusion of ipilimumab and/or BMS-986178 on the same day, the dose of ipilimumab and BMS-986178 should be replaced as soon as possible. In such instances, at least 19 days must elapse between the replacement dose of ipilimumab and the administration of the next dose of BMS-986178 and nivolumab combined with ipilimumab on a q3w schedule. However, if an ipilimumab-related infusion reaction prevents subsequent infusion of BMS-986178 on the same day, the dose of BMS-986178 should be replaced as soon as possible. In such instances, at least 19 days must elapse between the replacement dose of BMS-986178 and the administration of the next dose of BMS-986178 and nivolumab combined with ipilimumab.

Guidelines for management of an infusion reaction during study drug administration are included in Section 4.5.7.

4.5.6 Guidelines for Permanent Discontinuation

Subjects will be required to permanently discontinue all study drugs for the following AEs:

- Progressive Disease (see also Section 3.5.1 for details regarding continuing treatment beyond disease progression)
- Clinical deterioration, as assessed by the investigator
- Grade 3 infusion reaction that does not return to Grade 1 in less than 6 hours
- Grade 3 or greater pneumonitis, bronchospasm, myocarditis, neurologic toxicity, or cytokine release syndrome (i.e. systemic inflammatory response syndrome)
- Life-threatening skin toxicity (toxic epidermal necrolysis)
- Grade 2 or greater episcleritis, or iritis. Any Grade 2 or greater drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- Any Grade 4 AE; however, an exception may be made for the following upon consultation between the investigator and BMS medical monitor:
  - Grade 4 electrolyte abnormalities ≤ 72 hours in duration
  - Grade 4 neutropenia ≤ 7 days in duration
  - Grade 4 lymphopenia or leukopenia.
  - Grade 4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any toxicity that meets DLT criteria as defined in Section 4.5.1; however, an exception may be made on a case-by-case basis upon consultation between the investigator and BMS medical monitor:
  - Grade 3 diarrhea, nausea, vomiting, or abdominal pain that returns to Grade 1 or baseline within 3 days with medical intervention
  - AST or ALT > 5× and < 8× institutional ULN for < 2 weeks
  - Grade 3 pruritus or rash that returns to Grade 1 or baseline within 7 days with medical intervention

    The consideration to re-initiate study therapy under these exceptions will be made on a case-by-case basis after considering the overall risk/benefit profile and in consultation between the investigator and the Sponsor.
- Confirmed CR
- Completion of 24 weeks of treatment (Parts 1-7) or 24 months for Parts 8 and 9. Subjects in Part 2, 4 6, or 7 that continue for additional cycles up to 24 months of treatment.

All subjects who discontinue study drug(s) should comply with protocol-specified follow-up procedures as outlined in Section 5.1. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (eg, is imprisoned or involuntarily incarcerated for the treatment of a psychiatric or physical illness).

If study treatment is discontinued prior to the subject's completion of treatment, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate CRF page.

4.5.7 Treatment of Drug-Related Infusion Reactions

Since BMS-986178, nivolumab, and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if an infusion reaction or a hypersensitivity reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE v4.03 guidelines and reported on the appropriate CRF.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: Mild reaction; infusion interruption not indicated; intervention not indicated.

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg, to be given at least 30 minutes before additional study drug administrations.

For Grade 2 symptoms: Moderate reaction; requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours.

- Stop the drug being infused (either BMS-986178, nivolumab, or ipilimumab infusion), begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); monitor subject until resolution of symptoms.
- Bronchodilator or corticosteroid therapy may also be administered as appropriate.
- The infusion may be restarted at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely.
- The amount of study drug infused must be recorded on the CRF.
- If symptoms recur, then no further dosing with the relevant drug and/or subsequent drug, as the case may be, will be administered at that visit.

- The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional BMS-986178, nivolumab, or ipilimumab administrations (whichever caused the reaction). If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: Severe reaction; Grade 3: prolonged [eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated.

- Immediately discontinue study drug infusion. Begin an IV infusion of normal saline and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 0.5 mg (1:1,000 solution) for intramuscular administration or 0.1 to 0.25 mg (1:10,000 solution) injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug(s) will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

Late-occurring Symptoms:

In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Study drug will be administered in the clinical facility by trained medical personnel. The investigator and the study personnel will ensure that each subject receives the prescribed dose of study drug. Treatment compliance will be monitored by drug accountability as well as by recording BMS-986178, nivolumab, and/or ipilimumab administration in subjects' medical records and CRFs.

Drug supplies will be inventoried and accounted for throughout the study. The Drug Accountability Log will be reviewed by the study monitor during site visits and at the completion of the study. Any discrepancy should be brought to the attention of the Sponsor.

4.8 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials, and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS study monitor unless study drug containers must be immediately destroyed as required for safety or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures (SOPs) and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, (ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the monitor to review throughout the clinical trial period.

If conditions for on-site destruction cannot be met, the responsible BMS study monitor will make arrangements for the return of study drug to the Sponsor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible study monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.10 Retained Samples for Bioavailability/Bioequivalence

Not Applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures are presented in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, Table 5.1-6, Table 5.1-7, Table 5.1-8, and Table 5.1-9. In limited instances,

scheduled events can occur outside of the indicated timeframes; BMS should be notified of these instances.

Table 5.1-1: Screening Procedural Outline (CA012004) - Parts 1 - 9

Procedure	Screening Visit (-28 day to -1 Visit)	D -14 to -1 Visit	Notes
Eligibility Assessments			
Informed Consent	X		A subject is considered enrolled only when a protocol-specific informed consent is signed. Must be obtained prior to performing any screening procedures.
Inclusion/Exclusion Criteria	X		Must be confirmed prior to randomization or treatment assignment.
Medical History	X		Include any toxicities or allergy related to previous treatments.
Prior Cancer Therapies	X		
ECOG Performance Status	X		See Appendix 4.
Archived Tumor Tissue Sample	X		An archival, FFPE tumor tissue block, or slide samples (a minimum of 15 unstained slides [25 preferred]), may be provided by all subjects. Samples should be shipped to the central laboratory.
Fresh Pre-treatment Tumor Biopsy	X		**All subjects require a mandatory pre- and on-treatment biopsy.** **Archival specimens may not be substituted for fresh baseline specimens but can be submitted to help understand the evolution of the tumor (ie, PD-L1 expression changes over time).** For part 9, please refer to section 3.3.1-2)-2)(h)(ii)
Fecal Microbiome (Part 9 Only)	X		Subjects will receive kit during visit, collect sample at home and return to site.
Blood PD, Blood Genotype, and Blood TCR	X		
Safety Assessments			
Physical Examination (PE)	X		If the screening PE is performed within 24 hours prior to dosing on D1, then a single exam may count as both the screening and predose evaluations.
Physical Measurements	X		Includes height and weight.
Vital Signs	X		Includes body temperature, respiratory rate, seated blood pressure, and heart rate.
Oxygen Saturation	X		Pulse oximetry collected at rest.

Table 5.1-1: Screening Procedural Outline (CA012004) - Parts 1 - 9

Procedure	Screening Visit (-28 day to -1 Visit)	D -14 to -1 Visit	Notes
Electrocardiogram (ECGs)	X		ECGs should be recorded after the subject has been supine for at least 5 minutes. All ECG tests should be performed as a single measurement.
Laboratory Tests	Laboratory tests listed below must be completed within 2 weeks of D1 unless otherwise noted.		
Serology	X		Within 28 days of dosing, if required: Hep B surface antigen, and Hep C antibody (if Hep C antibody is positive reflex to Hep C RNA), or Hep C RNA. **Note**: Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements.
Chemistry (Excluding LFTs)		X	See Section 5.3.2. Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, carbon dioxide, phosphorus, BUN, creatinine, creatinine clearance, fasting glucose, total protein, albumin, amylase, lipase, uric acid, ferritin, CRP, and LDH.
CBC with Differential and Platelets		X	
LFT Assessment		X	See Section 5.3.2.
Urinalysis		X	See Section 5.3.2.
Thyroid Function Tests (TFTs)		X	TSH with free T3 and free T4.
Genetic Mutations	X		See Section 5.7. Collected as part of the medical history on appropriate CRF
Tumor Markers (Serum)	X		CA125, AFP, CEA, CA19-9, and PSA for all subjects
Pregnancy Test		X	For WOCBP only; serum will be collected at **screening and within 24 hours prior to dosing**. The serum pregnancy test may be completed on the first day of treatment, provided the results are available before the start of study therapy. If performed within 24 hours of dosing on C1D1, then C1D1 pregnancy test is not required.
Follicle Stimulating Hormone (FSH)	X		If needed to document post-menopausal status as defined in Section 3.3.3.
[redacted]		[redacted]	[redacted]

Table 5.1-1: Screening Procedural Outline (CA012004) - Parts 1 - 9

Procedure	Screening Visit (-28 day to -1 Visit)	D -14 to -1 Visit	Notes
Adverse Event Reporting			
Clinical Complaints		X	Collected during the 2 weeks prior to C1D1.
Monitor for Serious Adverse Events and any AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection	X		All SAEs must be collected from the date of the subject's written consent until 100 days of discontinuation of dosing. SAEs should be approved in eCRF directly within 5 business days of entry.
Efficacy Assessments			
Tumor Assessments	X		CT with contrast is the preferred modality (MRI if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum and should include other anatomic regions as indicated by individual subject disease histories.
Brain Imaging	X		Brain imaging (CT/MRI) for subjects with history or symptoms of brain metastases and who have not had brain imaging within 30 days of anticipated first study drug administration.
Bone Scan	X		As clinically indicated (eg, subjects with history or symptoms of bone metastases), but bone scans will not be considered a modality for the assessment for measurable disease.
IRT Subject Assignment/ Treatment Assignment	X	X	After the subject consents, the sites will use the IRT to have the subject number assigned. After the subject has completed all screening procedures, IRT will be used for treatment assignment or discontinuing the subject. Subsequent visits will need to be registered into the IRT system for drug supply. Participant must receive the first dose of study medication within 3 calendar days from treatment/cohort assignment.

Abbreviations: AFP = alpha fetal protein; BUN = blood urea nitrogen; C = Cycle; CEA = carcinoembryonic antigen; CBC = complete blood count; CRC = colorectal cancer; CRF = case report form; CRP = C-reactive protein; CT = computed tomography; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed, paraffin-embedded; HIV = human immunodeficiency virus; HPV = Human papillomavirus; IRT = Interactive Response Technology; LDH = lactic acid dehydrogenase; LFT =liver function test; MSI = microsatellite instability; MRI = magnetic resonance imaging; PD = pharmacodynamic; PSA = Prostate-Specific Antigen; RNA = ribonucleic acid; T3 =triiodothyronine; T4 = thyroxine; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; WOCBP = women of child bearing potential.

Table 5.1-2: On Treatment Procedural Outline Parts 1 and 2 (CA012004 - q2w Dosing)

(C1-C12, Additional Cycles) Cycle = 2 Weeks	C1			C2-C8	C9	C10 - beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Safety Assessments								
Physical Examination (PE)	X						X	Predose (C1 only); See note in screening.
Symptom-directed PE		X	X	X	X	X		To include signs and symptoms
Physical Measurements	X			X	X	X		Weight only
Vital Signs	X	X		X	X	X	X	See note in screening.[e] Observe subjects 4 hours post-infusion C1D1 and C2D1
12-Lead Electrocardiogram (ECG)	X				X			All ECG tests should be performed as a single measurement. ECGs will be done at both predose and 4 hours when BMS-986178 PK sample is collected (ECGs should be done prior to the PK sample) at C1D1 and C9D1.
Laboratory Tests	See note in screening procedures and Section 5.3.2. Predose on D1.							
Chemistry (Excluding LFTs)	X	X	X	X	X	X	X	**Collect on C1D1, C1D2 and C1D8 and every cycle D1**
CBC with Differential and Platelets	X	X	X	X	X	X	X	
LFT Assessment	X	X	X	X	X	X	X	AST, ALT, ALP, and T. Bilirubin. Direct Bilirubin (only if T. Bilirubin is elevated);

Table 5.1-2: On Treatment Procedural Outline Parts 1 and 2 (CA012004 - q2w Dosing)

(C1-C12, Additional Cycles) Cycle = 2 Weeks	C1			C2-C8	C9	C10 - beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
								GGT (if ALP increase is clinically significant)
Thyroid Test	X			X	X	X	X	TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration. **Every odd cycle D1**
Tumor Markers	X			X	X	X	X	eg, CA125, AFP, CEA, CA19-9, and PSA for subjects with qualifying tumors **Every odd cycle D1**
Urinalysis	As clinically indicated. See Section 5.3.2.							
Pregnancy Test[f]	X			X	X	X	X	
Adverse Event (AE) Reporting								
[redacted]	[redacted]							
Monitor for Non-Serious Adverse Events	Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.							
Monitor for Serious Adverse Events	See note in screening procedures (Table 5.1-1).							

Table 5.1-2: On Treatment Procedural Outline Parts 1 and 2 (CA012004 - q2w Dosing)

(C1-C12, Additional Cycles) Cycle = 2 Weeks	C1			C2-C8	C9	C10 - beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Pharmacokinetic Assessments	See Table 5.5.1-1 for specific samples at each cycle during the study							
Serial Serum PK Sampling for BMS-986178	See Table 5.5.1-1for specific samples at each cycle during the study.							
BMS-986178 ADA Sample	See Table 5.5.1-1 for specific samples at each cycle during the study							
Serial Serum PK Sampling for Nivolumab (Part 2 Only)	See Table 5.5.1-1 for specific samples at each cycle during the study							
Nivolumab ADA Sample (Part 2 Only)	See Table 5.5.1-1 for specific samples at each cycle during the study							
Biomarker Assessments	See Table 5.6-1 for specific samples at each cycle during the study.							
Blood RNA, Blood RO	See Table 5.6-1 for specific samples at each cycle during the study.							
Blood PD	See Table 5.6-1 for specific samples at each cycle during the study.							
PBMC	See Table 5.6-1 for specific samples at each cycle during the study.							
Blood Multiparameter Flow	See Table 5.6-1 for specific samples at each cycle during the study.							
Serum Factors	See Table 5.6-1 for specific samples at each cycle during the study.							
PD Plasma	See Table 5.6-1 for specific samples at each cycle during the study.							

Table 5.1-2: On Treatment Procedural Outline Parts 1 and 2 (CA012004 - q2w Dosing)

(C1-C12, Additional Cycles) Cycle = 2 Weeks	C1			C2-C8	C9	C10 - beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Mandatory Fresh Tumor Biopsy	See Table 5.6-1 for specific samples at each cycle during the study.							
Blood TCR	See Table 5.6-1 for specific samples at each cycle during the study.							
Efficacy Assessments								
Tumor Assessments	Every 8 weeks (± 1 week)						X	By methods used at baseline. Same modality should be used for all assessments. Assessed by RECIST v1.1; see Appendix 3. Assessment to be performed prior to initiating next cycle of treatment. An unconfirmed PR or unconfirmed CR must be confirmed at least 4 weeks after initial assessment.
Brain Imaging	As clinically indicated							
Bone Scan	As clinically indicated							
Clinical Drug Supplies								
Parts 1 and 2 BMS-986178	X			X	X	X		Supplied by BMS Use vials assigned per IRT
Part 2 **ONLY** Nivolumab (240 mg Flat Dose)	X			X	X	X		Supplied by BMS Use vials assigned per IRT

Abbreviations: ADA = anti-drug antibody; AFP = alpha fetal protein; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BMS = Bristol-Myers Squibb; C = Cycle; CBC = complete blood count; CEA = carcinoembryonic antigen; CR = complete response; CRC = colorectal cancer; D = Day; EOT = end of treatment; LFT = liver function test; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IRT = Interactive Response Technology; LFT = liver function test; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PR = partial response; PSA

= Prostate-Specific Antigen; RNA = ribonucleic acid; RO = receptor occupancy; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; VS = vital signs.

[a] EOT is defined as the visit where the decision is made to discontinue the subject from treatment.

[b] For subjects who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C12D14) and the start of the Week 1 Safety Follow-up visit.

[c] For subjects who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated and will be considered the start of the Week 1 Safety Follow-up visit.

[d] Subjects will have procedures listed in this table completed at all cycles. For these treatment groups, 1 cycle = 2 weeks, up to 12 cycles of dosing. Subjects who have additional cycles will follow this same time and events table.

[e] For BMS-986178, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion except for C1D1 and C2D1 (where vital signs will be obtained every 30 minutes until 4 hours post infusion). For nivolumab, vital signs will be obtained before the infusion and then every 30 minutes (± 10 minutes) until the start of BMS-986178 infusion or per institution guidelines for administration of nivolumab. The 30-minute post nivolumab infusion VS may correspond to the pre-infusion BMS-986178 VS. In the event BMS-986178 administration is delayed, nivolumab vital signs will be obtained until 60 minutes after completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.

[f] Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If the pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue and immediately notify the BMS Medical Monitor/designee per Section 6.4.

Table 5.1-3: On Treatment Procedural Outline Parts 3 and 5 (CA012004 - q3w Dosing)

(C1-C8, Additional Cycles) Cycle = 3 weeks	C1				C2-C3	C4	C5-beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Safety Assessments									
Physical Examination (PE)	X							X	Predose (C1 Only) See note in screening
Symptom-directed PE		X	X	X	X	X	X		To include signs and symptoms
Physical Measurements	X				X	X	X		Weight only
Vital Signs	X	X			X	X	X	X	See note in screening.[e] Observe subjects 4 hours post-infusion C1D1 and C2D1
12-Lead Electrocardiogram (ECGs)	X					X			All ECG tests should be performed as a single measurement. ECGs will be done at both predose and 4 hours when BMS-986178 PK sample is collected (ECGs should be done prior to the PK sample) at C1D1 and C4D1.
Laboratory Tests	See note in screening procedures and Section 5.3.2. Predose on D1.								
Chemistry (Excluding LFTs)	X	X	X	X	X	X	X	X	Collect on C1D1, C1D2, C1D8, and C1D15, and every cycle D1
CBC with Differential and Platelets	X	X	X	X	X	X	X	X	
LFT Assessment	X	X	X	X	X	X	X	X	AST, ALT, ALP, and T. Bilirubin. Direct Bilirubin (only if T. Bilirubin is elevated);

Table 5.1-3: On Treatment Procedural Outline Parts 3 and 5 (CA012004 - q3w Dosing)

(C1-C8, Additional Cycles) Cycle = 3 weeks	C1				C2-C3	C4	C5-beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
									GGT (if ALP increase is clinically significant
Thyroid Test	X				X		X	X	To include TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration. **Every odd cycle D1**
Tumor Markers	X				X	X	X	X	eg, CA125, AFP, CEA, CA19-9, and PSA for subjects with qualifying tumors **Every odd cycle D1**
Urinalysis	As clinically indicated. See Section 5.3.2.								
Pregnancy Test[f]	X				X	X	X	X	
Adverse Event Reporting									
[redacted]	[redacted]								
Monitor for Non-Serious Adverse Events	Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.								
Monitor for Serious Adverse Events	See note in screening procedures (Table 5.1-1).								

Table 5.1-3: On Treatment Procedural Outline Parts 3 and 5 (CA012004 - q3w Dosing)

(C1-C8, Additional Cycles) Cycle = 3 weeks	C1				C2-C3	C4	C5-beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Pharmacokinetic Assessments	See Table 5.5.1-3								
Serial Serum PK Sampling BMS-986178	Refer to Table 5.5.1-3.								
BMS-986178 ADA Sampling	Refer to Table 5.5.1-3.								
Serial Serum PK Sampling for Ipilimumab	Refer to Table 5.5.1-3.								
Ipilimumab ADA sampling	Refer to Table 5.5.1-3.								
Biomarker Assessments	See Table 5.6-2 for specific samples at each cycle during the study.								
Blood RNA, Blood RO	See Table 5.6-2 for specific samples at each cycle during the study.								
Blood PD	See Table 5.6-2 for specific samples at each cycle during the study.								
PBMC	See Table 5.6-2 for specific samples at each cycle during the study.								
Blood Multiparameter Flow	See Table 5.6-2 for specific samples at each cycle during the study.								
Serum Factors	See Table 5.6-2 for specific samples at each cycle during the study.								
PD Plasma	See Table 5.6-2 for specific samples at each cycle during the study.								

Table 5.1-3: On Treatment Procedural Outline Parts 3 and 5 (CA012004 - q3w Dosing)

(C1-C8, Additional Cycles) Cycle = 3 weeks	C1				C2-C3	C4	C5-beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Mandatory Fresh Tumor Biopsy	See Table 5.6-2 for specific samples at each cycle during the study.								
Blood TCR	See Table 5.6-2 for specific samples at each cycle during the study.								
Efficacy Assessments									
Tumor Assessments	Every 8 weeks (± 1 week) Note: If subject completes 24 weeks of dosing, C8D21 will be the last cycle visit (EOT), this will be at Week 25, and the 27-week scan should be done at this time.							X	By methods used at baseline. Same modality should be used for all assessments. Assessed by RECIST v1.1; see Appendix 3. Assessment to be performed prior to initiating next cycle of treatment. An unconfirmed PR or unconfirmed CR must be confirmed at least 4 weeks after initial assessment.
Brain Imaging	As clinically indicated								
Bone Scan	As clinically indicated								
Clinical Drug Supplies									
BMS-986178	X				X	X	X		All subjects Supplied by BMS Use vials assigned per IRT
Part 3 Ipilimumab (1 mg/kg)	X				X	X			Supplied by BMS Use vials assigned per IRT

Table 5.1-3: On Treatment Procedural Outline Parts 3 and 5 (CA012004 - q3w Dosing)

(C1-C8, Additional Cycles) Cycle = 3 weeks	C1				C2-C3	C4	C5-beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Part 5 Ipilimumab (3 mg/kg)	X				X	X			Supplied by BMS Use vials assigned per IRT

Abbreviations: ADA = anti-drug antibody; AFP = alpha fetal protein; BMS = Bristol-Myers Squibb; C=Cycle; CBC = complete blood count; CEA = carcinoembryonic antigen; CR = complete response; CRC = colorectal cancer; D = Day; ECG = electrocardiogram; EOT = end of treatment; LFT = liver function test; IRT = Interactive Response Technology; LFT = liver function test; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PR = partial response; PSA = Prostate-Specific Antigen; RNA = ribonucleic acid; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; VS = vital signs.

[a] EOT is defined as the visit where the decision is made to discontinue the subject from treatment.

[b] For subjects who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C8D21) and the start of the Week 1 Safety Follow-up visit.

[c] For subjects who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated and will be considered the start of the Week 1 Safety Follow-up visit.

[d] Subjects will have procedures listed in this table completed at all cycles. For these treatment groups 1 cycle = 3 weeks, up to 8 cycles of dosing. Subjects who have additional cycles will follow this same time and events table.

[e] For BMS-986178, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion except for C1D1 and C2D1 (where vital signs will be obtained every 30 minutes until 4 hours post infusion). Vital signs will be obtained before the infusion and then every 30 minutes (± 10 minutes) until the start of BMS-986178 infusion or per institution guidelines for administration of ipilimumab. The 30-minute post ipilimumab infusion VS may correspond to the pre-infusion BMS-986178 VS. In the event BMS-986178 administration is delayed, ipilimumab vital signs will be obtained until 60 minutes after completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.

[f] Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If the pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue and immediately notify the BMS Medical Monitor/designee per Section 6.4.

Table 5.1-4: On Treatment Procedural Outline Part 4, (CA012004 - q4w Dosing)

(C1-C6, Additional Cycles) Cycle = 4 weeks	C1				C2-C4		C5	C6-beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Safety Assessments										
Physical Examination (PE)	X								X	Predose (C1 only). See note in screening.
Symptom-directed PE		X	X	X	X	X	X	X		To include signs and symptoms
Physical Measurements	X				X		X	X		Weight only
Vital Signs	X	X			X		X	X	X	See note in screening.[e] Observe subjects 4 hours post-infusion C1D1 and C2D1
12-Lead Electrocardiogram (ECGs)	X						X			All ECG tests should be performed as a single measurement. ECGs will be done at both predose and 4 hours when BMS-986178 PK sample is collected (ECGs should be done prior to the PK sample) at C1D1 and C5D1.
Laboratory Tests	See note in screening procedures and Section 5.3.2. Predose on D1.									
Chemistry (Excluding LFTs)	X	X	X	X	X	X	X	X	X	
CBC with Differential and Platelets	X	X	X	X	X	X	X	X	X	

Table 5.1-4: On Treatment Procedural Outline Part 4, (CA012004 - q4w Dosing)

(C1-C6, Additional Cycles) Cycle = 4 weeks	C1				C2-C4		C5	C6-beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
LFT Assessment	X	X	X	X	X	X	X	X	X	AST, ALT, ALP, and T. Bilirubin. Direct Bilirubin (only if T. Bilirubin is elevated); GGT (if ALP increase is clinically significant)
Thyroid Test	X				X		X	X	X	TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Tumor Markers	X				X		X	X	X	eg, CA125, AFP, CEA, CA19-9, and PSA for subjects with qualifying tumors **Every odd cycle D1**
Urinalysis	As clinically indicated. See Section 5.3.2									
Pregnancy Test[f]	X				X		X	X	X	
Adverse Event Reporting										
[redacted]	[redacted]									
Monitor for Non-Serious Adverse Events	Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.									
Monitor for Serious Adverse Events	See note in screening procedures (Table 5.1-1).									

Table 5.1-4: On Treatment Procedural Outline Part 4, (CA012004 - q4w Dosing)

(C1-C6, Additional Cycles) Cycle = 4 weeks	C1				C2-C4		C5	C6-beyond		Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Pharmacokinetic Assessments	See Table 5.5.1-2 for specific samples at each cycle during the study.									
Serial Serum PK Sampling BMS-986178	See Table 5.5.1-2 for specific samples at each cycle during the study.									
BMS-986178 ADA Sample	See Table 5.5.1-2 for specific samples at each cycle during the study.									
Serial Serum PK Sampling for Nivolumab	See Table 5.5.1-2 for specific samples at each cycle during the study.									
Nivolumab ADA Sampling	See Table 5.5.1-2 for specific samples at each cycle during the study.									
Biomarker Assessments	See Table 5.6-3 for specific samples at each cycle during the study.									
Blood RNA, Blood RO	See Table 5.6-3 for specific samples at each cycle during the study.									
Blood PD	See Table 5.6-3 for specific samples at each cycle during the study.									
PBMC	See Table 5.6-3 for specific samples at each cycle during the study.									
Blood Multiparameter Flow	See Table 5.6-3 for specific samples at each cycle during the study.									
Serum Factors	See Table 5.6-3 for specific samples at each cycle during the study.									
PD Plasma	See Table 5.6-3 for specific samples at each cycle during the study.									

Table 5.1-4: On Treatment Procedural Outline Part 4, (CA012004 - q4w Dosing)

(C1-C6, Additional Cycles) Cycle = 4 weeks	**C1**				**C2-C4**		**C5**	**C6-beyond**		**Window (± 2 days)**
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**EOT[a,b,c]**	**Notes[d]**
Mandatory Fresh Tumor Biopsy	See Table 5.6-3 for specific samples at each cycle during the study.									
Blood TCR	See Table 5.6-3 for specific samples at each cycle during the study.									
Efficacy Assessments										
Tumor Assessments	Every 8 weeks (± 1 week)								X	By methods used at baseline. Same modality should be used for all assessments. Assessed by RECIST v1.1; see Appendix 3. Assessment to be performed prior to initiating next cycle of treatment. An unconfirmed PR or unconfirmed CR must be confirmed at least 4 weeks after initial assessment.
Brain Imaging	As clinically indicated									
Bone Scan	As clinically indicated									
Clinical Drug Supplies										
BMS-986178	X				X		X	X		Supplied by BMS Use vials assigned per IRT
Nivolumab	X				X		X	X		Supplied by BMS Use vials assigned per IRT

Abbreviations: ADA = anti-drug antibody; AFP = alpha fetal protein; BMS = Bristol-Myers Squibb; C = Cycle; CBC = complete blood count; CEA = carcinoembryonic antigen; CR = complete response; CRC = colorectal cancer; D = Day; EOT = end of treatment; LFT = liver function test; IRT = Interactive Response Technology; LFT = liver function test; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PR = partial response; PSA = Prostate-Specific Antigen; RNA = ribonucleic acid; RO = receptor occupancy; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; VS = vital signs.

[a] EOT is defined as the visit where the decision is made to discontinue the subject from treatment.

[b] For subjects who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C6D28) and the start of the Week 1 Safety Follow-up visit.

[c] For subjects who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated and will be considered the start of the Week 1 Safety Follow-up visit.

[d] Subjects will have procedures listed in this table completed at all cycles. For these treatment groups 1 cycle = 4 weeks, up to 6 cycles of dosing. Subjects who have additional cycles will follow this same time and events table.

[e] For BMS-986178, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion except for C1D1 and C2D1 (where vital signs will be obtained every 30 minutes until 4 hours post infusion). For nivolumab, vital signs will be obtained before the infusion and then every 30 minutes (± 10 minutes) until the start of BMS-986178 infusion or per institution guidelines for administration of nivolumab. The 30-minute post nivolumab infusion VS may correspond to the pre-infusion BMS-986178 VS. In the event BMS-986178 administration is delayed, nivolumab vital signs will be obtained until 60 minutes after completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.

[f] Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If the pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue and immediately notify the BMS Medical Monitor/designee per Section 6.4.

Table 5.1-5: On Treatment Procedural Outline Part 6 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with RCC)

(C1-C7, Additional Cycles) Cycle = 3 weeks for C1-C4 Cycle = 4 weeks for C5 and beyond	C1				C2-C3	C4	C5-Beyond			Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**D15**	**EOT[a,b,c]**	**Notes[d]**
Safety Assessments										
Physical Examination (PE)	X								X	Predose (C1 Only) See note in screening
Symptom-directed PE		X	X	X	X	X	X	X		To include signs and symptoms
Physical Measurements	X				X	X	X			Weight only
Vital Signs	X	X			X	X	X		X	See note in screening.[e] Observe subjects 4 hours post-infusion C1D1 and C2D1
12-Lead Electrocardiogram (ECGs)	X					X				All ECG tests should be performed as a single measurement. ECGs will be done at both predose and 4 hours when BMS-986178 PK sample is collected (ECGs should be done prior to the PK sample) on C1D1 and C4D1.
Laboratory Tests	See note in screening procedures and Section 5.3.2. Predose on D1.									
Chemistry (Excluding LFTs)	X	X	X	X	X	X	X	X	X	

Table 5.1-5: On Treatment Procedural Outline Part 6 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with RCC)

(C1-C7, Additional Cycles) Cycle = 3 weeks for C1-C4 Cycle = 4 weeks for C5 and beyond	C1				C2-C3	C4	C5-Beyond			Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**D15**	**EOT[a,b,c]**	**Notes[d]**
CBC with Differential and Platelets	X	X	X	X	X	X	X	X	X	
LFT Assessment	X	X	X	X	X	X	X	X	X	AST, ALT, ALP, and T. Bilirubin. Direct Bilirubin (only if T. Bilirubin is elevated); GGT (if ALP increase is clinically significant)
Thyroid Test	X				X		X		X	TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration. **Every odd cycle D1**
Urinalysis	As clinically indicated. See Section 5.3.2.									
Pregnancy Test[f]	X				X	X	X		X	
Adverse Event Reporting										
[redacted]	[redacted]									

Table 5.1-5: On Treatment Procedural Outline Part 6 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with RCC)

(C1-C7, Additional Cycles) Cycle = 3 weeks for C1-C4 Cycle = 4 weeks for C5 and beyond	C1				C2-C3	C4	C5-Beyond			Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**D15**	**EOT[a,b,c]**	**Notes[d]**
Monitor for Non-Serious Adverse Events	Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.									
Monitor for Serious Adverse Events	See note in screening procedures (Table 5.1-1)									
Pharmacokinetic Assessments	See Table 5.5.1-4 for specific samples at each cycle during the study.									
Serial Serum PK Sampling BMS-986178	See Table 5.5.1-4 for specific samples at each cycle during the study.									
BMS-986178 ADA Sampling	See Table 5.5.1-4 for specific samples at each cycle during the study.									
Serial Serum PK Sampling for Nivolumab	See Table 5.5.1-4 for specific samples at each cycle during the study.									
Nivolumab ADA Sampling	See Table 5.5.1-4 for specific samples at each cycle during the study.									
Serial Serum PK Sampling for Ipilimumab	See Table 5.5.1-4 for specific samples at each cycle during the study.									

Table 5.1-5: On Treatment Procedural Outline Part 6 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with RCC)

(C1-C7, Additional Cycles) Cycle = 3 weeks for C1-C4 Cycle = 4 weeks for C5 and beyond	C1				C2-C3	C4	C5-Beyond			Window (± 2 days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**D15**	**EOT[a,b,c]**	**Notes[d]**
Ipilimumab ADA sampling	See Table 5.5.1-4 for specific samples at each cycle during the study.									
Biomarker Assessments	See Table 5.6-2 for specific samples at each cycle during the study.									
Blood RNA, Blood RO	See Table 5.6-2 for specific samples at each cycle during the study.									
Blood PD	See Table 5.6-2 for specific samples at each cycle during the study.									
PBMC	See Table 5.6-2 for specific samples at each cycle during the study.									
Blood Multiparameter Flow	See Table 5.6-2 for specific samples at each cycle during the study.									
Serum Factors	See Table 5.6-2 for specific samples at each cycle during the study.									
PD Plasma	See Table 5.6-2 for specific samples at each cycle during the study.									
Mandatory Fresh Tumor Biopsy	See Table 5.6-2 for specific samples at each cycle during the study.									
Blood TCR	See Table 5.6-2 for specific samples at each cycle during the study.									

Table 5.1-5: On Treatment Procedural Outline Part 6 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with RCC)

(C1-C7, Additional Cycles) Cycle = 3 weeks for C1-C4 Cycle = 4 weeks for C5 and beyond	**C1**				**C2-C3**	**C4**	**C5-Beyond**			**Window (± 2 days)**
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**D15**	**EOT[a,b,c]**	**Notes[d]**
Efficacy Assessments										
Tumor Assessments	Every 8 weeks (± 1 week) Note: If subject completes 24 weeks of dosing, C7D21 will be the last cycle visit (EOT), this will be at Week 24, and the 27 week scan should be done at this time.									By methods used at baseline. Same modality should be used for all assessments. Assessed by RECIST v1.1; see Appendix 3. Assessment to be performed prior to initiating next cycle of treatment. An unconfirmed PR or unconfirmed CR must be confirmed at least 4 weeks after initial assessment.
Brain Imaging	As clinically indicated									
Bone Scan	As clinically indicated									
Clinical Drug Supplies										
BMS-986178 **(C1-C4, q3w; C5 and beyond, q4w)**	Dosing will be on C1D1, C2D1, C3D1, C4D1, C5D1, C6D1, and C7D1, which corresponds to Weeks 1, 4, 7, 10, 13, 17, and 21									Supplied by BMS Use vials assigned per IRT
Nivolumab (240 mg flat dose) **(C1-C4, q3w)**	Dosing will be on C1D1, C2D1, C3D1, and C4D1, which corresponds to Weeks 1, 4, 7, and 10									Supplied by BMS Use vials assigned per IRT

Table 5.1-5: On Treatment Procedural Outline Part 6 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with RCC)

(C1-C7, Additional Cycles) **Cycle = 3 weeks for C1-C4** **Cycle = 4 weeks for C5 and beyond**	**C1**				**C2-C3**	**C4**	**C5-Beyond**			**Window (± 2 days)**
Procedure	**D1**	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**D15**	**EOT[a,b,c]**	**Notes[d]**
Nivolumab (480 mg flat dose) **(C5 and beyond, q4w)**	Dosing will be on C5D1, C6D1, and C7D1, which corresponds to Weeks 13, 17, and 21									Supplied by BMS Use vials assigned per IRT
Ipilimumab (1 mg/kg) **(C1-C4, q3w)**	Dosing will be on C1D1, C2D1, C3D1, and C4D1, which corresponds to Weeks 1, 4, 7, and 10									Supplied by BMS Use vials assigned per IRT

Abbreviations: ADA = anti-drug antibody; AFP = alpha fetal protein; BMS = Bristol-Myers Squibb; C = Cycle; CBC = complete blood count; CEA = carcinoembryonic antigen; CR = complete response; CRC = colorectal cancer; D = Day; ECG = electrocardiogram; EOT = end of treatment; LFT = liver function test; IRT = Interactive Response Technology; LFT = liver function test; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PR = partial response; PSA = Prostate-Specific Antigen; RNA = ribonucleic acid; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; VS = vital signs.

[a] EOT is defined as the visit where the decision is made to discontinue the subject from treatment.

[b] For subjects who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C7D21) and the start of the Week 1 Safety Follow-up visit.

[c] For subjects who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated and will be considered the start of the Week 1 Safety Follow-up visit.

[d] Subjects will have procedures listed in this table completed at all cycles. For C1 to C4, 1 cycle = 3 weeks, and for C5 and beyond, 1 cycle = 4 weeks. Subjects who have additional cycles will follow this same time and events table.

[e] For BMS-986178, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion, except for C1D1 and C2D1 (where vital signs will be obtained every 30 minutes until 4 hours post infusion). Vital signs will be obtained before the infusion and

then every 30 minutes (± 10 minutes) until the start of the next study drug infusion or per institution guidelines for administration of ipilimumab and/or nivolumab. The 30-minute post nivolumab infusion VS may correspond to the pre-infusion ipilimumab or BMS-986178 VS and the 30-minute post ipilimumab infusion VS may correspond to the pre-infusion BMS-986178 VS. In the event the next study drug administration is delayed, nivolumab and/or ipilimumab vital signs will be obtained until 60 minutes after completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.

f Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If the pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue and immediately notify the BMS Medical Monitor/designee per Section 6.4.

Table 5.1-6: On Treatment Procedural Outline Part 7 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with NSCLC)

(C1-C4, Additional Cycles) (Cycle = 6 weeks)	C1						C2-C4			C5-Beyond				Window (± 2 Days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D22**	**D29**	**D1**	**D15**	**D29**	**D1**	**D15**	**D29**	**EOT a,b,c**	**Notes[d]**
Safety Assessments														
Physical Examination (PE)	X												X	Predose (C1 only); See note in screening.
Symptom-directed PE		X	X	X	X	X	X	X	X	X				To include signs and symptoms
Physical Measurements	X			X		X	X	X	X	X				Weight only
Vital Signs	X	X		X		X	X	X	X	X			X	See note in screening.[e] Observe subjects 4 hours post-infusion C1D1 and C2D1
12-Lead Electrocardiogram (ECG)	X						X							All ECG tests should be performed as a single measurement. ECGs will be done at both predose and 4 hours when BMS-986178 PK sample is collected (ECGs should be done prior to the PK sample) at C1D1 and C4D1.
Laboratory Tests	See note in screening procedures and Section 5.3.2. Predose on D1.													
Chemistry (Excluding LFTs)	X	X	X	X	X	X	X	X	X	X			X	
CBC with Differential and Platelets	X	X	X	X	X	X	X	X	X	X			X	

Table 5.1-6: On Treatment Procedural Outline Part 7 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with NSCLC)

(C1-C4, Additional Cycles) (Cycle = 6 weeks)	C1						C2-C4			C5-Beyond				Window (± 2 Days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D22**	**D29**	**D1**	**D15**	**D29**	**D1**	**D15**	**D29**	**EOT [a,b,c]**	**Notes[d]**
LFT Assessment	X	X	X	X	X	X	X	X	X	X			X	AST, ALT, ALP, and T. Bilirubin. Direct Bilirubin (only if T. Bilirubin is elevated); GGT (if ALP increase is clinically significant)
Thyroid Test	X						X			X			X	TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Urinalysis	As clinically indicated. See Section 5.3.2.													
Pregnancy Test[f]	X			X		X	X	X	X	X			X	
Adverse Event (AE) Reporting														
[redacted]	[redacted]													
Monitor for Non-Serious Adverse Events	Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.													
Monitor for Serious Adverse Events	See note in screening procedures (Table 5.1-1).													
Pharmacokinetic Assessments	See Table 5.5.1-5 for specific samples at each cycle during the study.													

Table 5.1-6: On Treatment Procedural Outline Part 7 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with NSCLC)

(C1-C4, Additional Cycles) (Cycle = 6 weeks)	C1						C2-C4			C5-Beyond				Window (± 2 Days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D22**	**D29**	**D1**	**D15**	**D29**	**D1**	**D15**	**D29**	**EOT a,b,c**	**Notes[d]**
Serial Serum PK Sampling for BMS-986178	See Table 5.5.1-5 for specific samples at each cycle during the study.													
BMS-986178 ADA Sample	See Table 5.5.1-5 for specific samples at each cycle during the study.													
Serial Serum PK Sampling for Nivolumab	See Table 5.5.1-5 for specific samples at each cycle during the study.													
Nivolumab ADA Sample	See Table 5.5.1-5 for specific samples at each cycle during the study.													
Serial Serum PK Sampling for Ipilimumab	See Table 5.5.1-5 for specific samples at each cycle during the study.													
Ipilimumab ADA Sample	See Table 5.5.1-5 for specific samples at each cycle during the study.													
Biomarker Assessments	See Table 5.6-4 for specific samples at each cycle during the study.													
Blood RNA, Blood RO	See Table 5.6-4 for specific samples at each cycle during the study.													
Blood PD	See Table 5.6-4 for specific samples at each cycle during the study.													
PBMC	See Table 5.6-4 for specific samples at each cycle during the study.													
Blood Multiparameter Flow	See Table 5.6-4 for specific samples at each cycle during the study.													

Table 5.1-6: On Treatment Procedural Outline Part 7 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with NSCLC)

(C1-C4, Additional Cycles) (Cycle = 6 weeks)	C1						C2-C4			C5-Beyond				Window (± 2 Days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D22**	**D29**	**D1**	**D15**	**D29**	**D1**	**D15**	**D29**	**EOT a,b,c**	**Notes[d]**
Serum Factors	See Table 5.6-4 for specific samples at each cycle during the study.													
PD Plasma	See Table 5.6-4 for specific samples at each cycle during the study.													
Mandatory Fresh Tumor Biopsy	See Table 5.6-4 for specific samples at each cycle during the study.													
Blood TCR	See Table 5.6-4 for specific samples at each cycle during the study.													
Efficacy Assessments														
Tumor Assessments	Every 8 weeks (± 1 week)												X	By methods used at baseline. Same modality/ should be used for all assessments. Assessed by RECIST v1.1; see Appendix 3. Assessment to be performed prior to initiating next cycle of treatment. An unconfirmed PR or unconfirmed CR must be confirmed at least 4 weeks after initial assessment.
Brain Imaging	As clinically indicated													
Bone Scan	As clinically indicated													
Clinical Drug Supplies														
BMS-986178 (q2w)	Dosing will be on C1D1, C1D15, C1D29, C2D1, C2D15, C2D29, C3D1, C3D15, C3D29, C4D1, C4D15, and C4D29, which corresponds to Weeks 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23									X	X	X		Supplied by BMS Use vials assigned per IRT

Table 5.1-6: On Treatment Procedural Outline Part 7 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with NSCLC)

(C1-C4, Additional Cycles) (Cycle = 6 weeks)	C1						C2-C4			C5-Beyond				Window (± 2 Days)
Procedure	**D1**	**D2**	**D8**	**D15**	**D22**	**D29**	**D1**	**D15**	**D29**	**D1**	**D15**	**D29**	**EOT [a,b,c]**	**Notes[d]**
Nivolumab (240 mg q2w Flat Dose)	Dosing will be on C1D1, C1D15, C1D29, C2D1, C2D15, C2D29, C3D1, C3D15, C3D29, C4D1, C4D15, and C4D29, which corresponds to Weeks 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23									X	X	X		Supplied by BMS Use vials assigned per IRT
Ipilimumab (1 mg/kg q6w)	Dosing will be on Day 1 of each cycle,									X				Supplied by BMS Use vials assigned per IRT

Abbreviations: ADA = anti-drug antibody; AFP = alpha fetal protein; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BMS = Bristol-Myers Squibb; C = Cycle; CBC = complete blood count; CEA = carcinoembryonic antigen; CR = complete response; CRC = colorectal cancer; D = Day; EOT = end of treatment; LFT = liver function test; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IRT = Interactive Response Technology; LFT = liver function test; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PR = partial response; PSA = Prostate-Specific Antigen; RNA = ribonucleic acid; RO = receptor occupancy; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; VS = vital signs.

[a] EOT is defined as the visit where the decision is made to discontinue the subject from treatment.

[b] For subjects who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C4D35) and the start of the Week 1 Safety Follow-up visit.

[c] For subjects who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated and will be considered the start of the Week 1 Safety Follow-up visit.

[d] Subjects will have procedures listed in this table completed at all cycles. One cycle = 6 weeks. Subjects who have additional cycles will follow this same time and events table. BMS-986178, nivolumab, and ipilimumab will continue for all additional cycles.

[e] For BMS-986178, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion, except for C1D1 and C2D1 (where vital signs will be obtained every 30 minutes until 4 hours post infusion). Vital signs will be obtained before the infusion and then every 30 minutes (± 10 minutes) until the start of the next study drug infusion or per institution guidelines for administration of ipilimumab and nivolumab. The 30-minute post nivolumab infusion VS may correspond to the pre-infusion ipilimumab VS and the 30-minute post ipilimumab infusion VS may correspond to the pre-infusion BMS-986178 VS. In the event the next study drug administration is delayed, nivolumab and/or ipilimumab vital signs will be obtained until

60 minutes after completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.

f Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If the pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue and immediately notify the BMS Medical Monitor/designee per Section 6.4.

Table 5.1-7: On Treatment Procedural Outline Part 8 (CA012004 - q12w Dosing)

(C1-C8) (Cycle = 12 weeks)	C1-C2					C3-beyond					Window (± 2 Days)
Procedure	**D1**	**D8**	**D15**	**D29**	**D57**	**D1**	**D15**	**D29**	**D57**	**EOT [a,b,c]**	**Notes[d]**
Safety Assessments											
Physical Examination (PE)	X		X							X	Predose (C1 only); See note in screening.
Symptom-directed PE		X		X	X	X	X	X	X		To include signs and symptoms;
Physical Measurements	X		X	X	X	X	X	X	X		Weight only
Vital Signs	X		X	X	X	X	X	X	X	X	See note in screening.[e] Observe subjects 4 hours post-infusion C1D1 and C2D1
12-Lead Electrocardiogram (ECG)	X										All ECG tests should be performed as a single measurement. ECGs will be done at both predose and 4 hours when BMS-986178 PK sample is collected (ECGs should be done prior to the PK sample) at C1D1 and C2D1.
Laboratory Tests	See note in screening procedures and Section 5.3.2. Predose on all dosing days										
Chemistry (Excluding LFTs)	X	X	X	X	X	X	X	X	X	X	
CBC with Differential and Platelets	X	X	X	X	X	X	X	X	X	X	

Table 5.1-7: On Treatment Procedural Outline Part 8 (CA012004 - q12w Dosing)

(C1-C8) (Cycle = 12 weeks)	C1-C2					C3-beyond					Window (± 2 Days)
Procedure	**D1**	**D8**	**D15**	**D29**	**D57**	**D1**	**D15**	**D29**	**D57**	**EOT a,b,c**	**Notes[d]**
LFT Assessment	X	X	X	X	X	X	X	X	X	X	AST, ALT, ALP, and T. Bilirubin. Direct Bilirubin (only if T. Bilirubin is elevated); GGT (if ALP increase is clinically significant)
Thyroid Test	X					X				X	TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Tumor Markers	X			X	X	X		X	X	X	
Urinalysis	As clinically indicated. See Section 5.3.2.										
Pregnancy Test[f]	X			X	X	X		X	X	X	
Adverse Event (AE) Reporting											
[redacted]			[redacted]								
Monitor for Non-Serious Adverse Events			Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.								
Monitor for Serious Adverse Events			See note in screening procedures (Table 5.1-1).								

Table 5.1-7: On Treatment Procedural Outline Part 8 (CA012004 - q12w Dosing)

(C1-C8) (Cycle = 12 weeks)	C1-C2					C3-beyond					Window (± 2 Days)
Procedure	**D1**	**D8**	**D15**	**D29**	**D57**	**D1**	**D15**	**D29**	**D57**	**EOT a,b,c**	**Notes[d]**
Pharmacokinetic Assessments			See Table 5.5.1-6 for specific samples at each cycle during the study.								
Serial Serum PK Sampling for BMS-986178 (cohort 1-3 only)			See Table 5.5.1-6 for specific samples at each cycle during the study.								
BMS-986178 ADA Sample (cohort 1-3 only)			See Table 5.5.1-6 for specific samples at each cycle during the study.								
Serial Serum PK Sampling for Nivolumab			See Table 5.5.1-6 for specific samples at each cycle during the study.								
Nivolumab ADA Sample			See Table 5.5.1-6 for specific samples at each cycle during the study.								
Biomarker Assessments			See Table 5.6-5 for specific samples at each cycle during the study.								
Blood RNA, Blood RO			See Table 5.6-5 for specific samples at each cycle during the study.								
Blood PD			See Table 5.6-5 for specific samples at each cycle during the study.								
PBMC			See Table 5.6-5 for specific samples at each cycle during the study.								
Blood Multiparameter Flow	See Table 5.6-5 for specific samples at each cycle during the study.										
Serum Factors	See Table 5.6-5 for specific samples at each cycle during the study.										

Table 5.1-7: On Treatment Procedural Outline Part 8 (CA012004 - q12w Dosing)

(C1-C8) (Cycle = 12 weeks)	**C1-C2**					**C3-beyond**					**Window (± 2 Days)**
Procedure	**D1**	**D8**	**D15**	**D29**	**D57**	**D1**	**D15**	**D29**	**D57**	**EOT [a,b,c]**	**Notes[d]**
PD Plasma	See Table 5.6-5 for specific samples at each cycle during the study.										
ctDNA	See Table 5.6-5 for specific samples at each cycle during the study.										
Mandatory Fresh Tumor Biopsy	See Table 5.6-5 for specific samples at each cycle during the study.										On treatment C1D15 and C1D78
Blood TCR	See Table 5.6-5 for specific samples at each cycle during the study.										
Efficacy Assessments											
Tumor Assessments	Every 12 weeks (± 1 week)									X	By methods used at baseline. Same modality/ should be used for all assessments. Assessed by RECIST v1.1; see Appendix 3. Assessment to be performed prior to initiating next cycle of treatment. An unconfirmed PR or unconfirmed CR must be confirmed at least 6 weeks after initial assessment.

Table 5.1-7: On Treatment Procedural Outline Part 8 (CA012004 - q12w Dosing)

(C1-C8) (Cycle = 12 weeks)	C1-C2					C3-beyond					Window (± 2 Days)
Procedure	**D1**	**D8**	**D15**	**D29**	**D57**	**D1**	**D15**	**D29**	**D57**	**EOT [a,b,c]**	**Notes[d]**
Brain Imaging	As clinically indicated										
Bone Scan	As clinically indicated										
Clinical Drug Supplies											
BMS-986178 (q12w) Cohort 1-3 Only	Dosing on Day 1 of each cycle										Supplied by BMS Use vials assigned per IRT
Nivolumab (480 mg Flat Dose q4w)	Dosing on Day 1, 29, and 57 of each cycle										Supplied by BMS Use vials assigned per IRT
Tetanus Vaccine	C1D1 Only										Locally Sourced

Abbreviations: ADA = anti-drug antibody; AFP = alpha fetal protein; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BMS = Bristol-Myers Squibb; C = Cycle; CBC = complete blood count; CEA = carcinoembryonic antigen; CR = complete response; CRC = colorectal cancer; D = Day; EOT = end of treatment; LFT = liver function test; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IRT = Interactive Response Technology; LFT = liver function test; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PR = partial response; PSA = Prostate-Specific Antigen; RNA = ribonucleic acid; RO = receptor occupancy; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; VS = vital signs.

[a] EOT is defined as the visit where the decision is made to discontinue the subject from treatment.

[b] For subjects who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C9D78) and the start of the Week 1 Safety Follow-up visit.

[c] For subjects who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated and will be considered the start of the Week 1 Safety Follow-up visit.

[d] Subjects will have procedures listed in this table completed at all cycles. One cycle = 12 weeks.

[e] For BMS-986178, vital signs will be obtained before the infusion and then every 15 minutes (±5 minutes) until 60 minutes after completion of the infusion, except for C1D1 and C2D1 (where vital signs will be obtained every 30 minutes until 4 hours post infusion). Vital signs will be obtained before the infusion and

then every 30 minutes (±10 minutes) until the start of the next study drug infusion or per institution guidelines for administration of nivolumab. The 30-minute post nivolumab infusion VS may correspond to the pre-infusion BMS-986178 VS. In the event the next study drug administration is delayed, nivolumab vital signs will be obtained until 60 minutes after completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.

[f] Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If the pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue and immediately notify the BMS Medical Monitor/designee per Section 6.4.

Table 5.1-8: On Treatment Procedural Outline Part 9 (CA012004 - q4w Dosing)

(C1-C26) (Cycle = 4 weeks)	C1				**C2-beyond**			**Window (± 2 Days)**
Procedure	D-3	D1	D8	D15	D1	C2D15 Only	EOT [a,b,c]	Notes[d]
Safety Assessments								
Physical Examination (PE)		X					X	Predose (C1 only); See note in screening.
Symptom-directed PE			X	X	X	X		To include signs and symptoms
Physical Measurements	X	X			X			Weight only
Vital Signs		X	X	X	X	X	X	See note in screening.[e]
12-Lead Electrocardiogram (ECG)		X			X (C5D1 only)			All ECG tests should be performed as a single measurement. ECGs will be done at predose at C1D1 and C5D1.
Laboratory Tests	See note in screening procedures and Section 5.3.2. Predose on all dosing days							
Chemistry (Excluding LFTs)		X	X	X	X	X	X	
CBC with Differential and Platelets	X	X	X	X	X	X	X	
LFT Assessment		X	X	X	X	X	X	AST, ALT, ALP, and T. Bilirubin. Direct Bilirubin (only if T. Bilirubin is elevated); GGT (if ALP increase is clinically significant)

Table 5.1-8: On Treatment Procedural Outline Part 9 (CA012004 - q4w Dosing)

(C1-C26) (Cycle = 4 weeks)	C1				C2-beyond			Window (± 2 Days)
Procedure	D-3	D1	D8	D15	D1	C2D15 Only	EOT a,b,c	Notes[d]
Thyroid Test		X			X		X	TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Urinalysis	X	As clinically indicated. See Section 5.3.2						
Pregnancy Test[f]	X				X		X	
Adverse Event (AE) Reporting								
[redacted]		[redacted]						
Monitor for Non-Serious Adverse Events		Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.						
Monitor for Serious Adverse Events and any AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection		See note in screening procedures (Table 5.1-1).						
Pharmacokinetic Assessments		See Table Table 5.5.1-7 for specific samples at each cycle during the study.						
Serial Serum PK Sampling for BMS986178		See Table Table 5.5.1-7 for specific samples at each cycle during the study.						

Table 5.1-8: On Treatment Procedural Outline Part 9 (CA012004 - q4w Dosing)

(C1-C26) (Cycle = 4 weeks)	C1				**C2-beyond**			**Window (± 2 Days)**
Procedure	D-3	D1	D8	D15	D1	C2D15 Only	EOT [a,b,c]	Notes[d]
BMS-986178 ADA Sample		See Table Table 5.5.1-7 for specific samples at each cycle during the study.						
Serial Serum PK Sampling for Nivolumab		See Table Table 5.5.1-7 for specific samples at each cycle during the study.						
Nivolumab ADA Sample		See Table Table 5.5.1-7 for specific samples at each cycle during the study.						
Biomarker Assessments	See Table 5.6-6 for specific samples at each cycle during the study.							
Fecal Microbiome	See Table 5.6-6 for specific samples at each cycle during the study.							
Blood RNA	See Table 5.6-6 for specific samples at each cycle during the study.							
Blood PD	See Table 5.6-6 for specific samples at each cycle during the study.							
PBMC	See Table 5.6-6 for specific samples at each cycle during the study.							
Blood Multiparameter Flow	See Table 5.6-6 for specific samples at each cycle during the study.							
Serum Factors	See Table 5.6-6 for specific samples at each cycle during the study.							
PD Plasma	See Table 5.6-6 for specific samples at each cycle during the study.							
Mandatory Fresh Tumor Biopsy	See Table 5.6-6 for specific samples at each cycle during the study.							
Blood TCR	See Table 5.6-6 for specific samples at each cycle during the study.							
Efficacy Assessments								

Table 5.1-8: On Treatment Procedural Outline Part 9 (CA012004 - q4w Dosing)

(C1-C26) **(Cycle = 4 weeks)**	C1				**C2-beyond**			**Window (± 2 Days)**
Procedure	D-3	D1	D8	D15	D1	C2D15 Only	EOT [a,b,c]	Notes[d]
Tumor Assessments	Every 8 weeks (± 1 week)						X	By methods used at baseline. Same modality/ should be used for all assessments. Assessed by RECIST v1.1; see Appendix 3. Assessment to be performed prior to initiating next cycle of treatment. An unconfirmed PR or unconfirmed CR must be confirmed at least 6 weeks after initial assessment.
Brain Imaging	As clinically indicated							
Bone Scan	As clinically indicated							
Clinical Drug Supplies								
BMS986178 40 mg flat dose (q4w)	Cohort 1: Dosing on Day 1 of C1 through C6, C9, C12 Cohort 2: Not applicable							Supplied by BMS Use vials assigned per IRT
Nivolumab (240 mg Flat Dose) (480 mg Flat Dose q4w)	C1D15 as a 240 mg flat dose (initial dose) Starting on C2D1 as 480 mg flat dose q4w							Supplied by BMS Use vials assigned per IRT
Cyclophosphamide (300 mg/m^2)	Day -3 prior to C1D1 only							Sourced locally
UbiLT3 and/or UbiLT6 (0.5 mg or 1 mg)	C1D1 0.5 mg UbiLT3 and 0.5 mg UbiLT6 Intranodally (2 different lymph nodes) C1D8 0.5 mg UbiLT3 and 0.5 mg UbiLT6 Intradermal							Sourced by BMS

Table 5.1-8: On Treatment Procedural Outline Part 9 (CA012004 - q4w Dosing)

(C1-C26) (Cycle = 4 weeks)	C1				**C2-beyond**			**Window (± 2 Days)**
Procedure	D-3	D1	D8	D15	D1	C2D15 Only	EOT [a,b,c]	Notes[d]
	Starting at C1D15, alternating 1 mg UbiLT3 or 1 mg UbiLT6 will be given Intradermal q2w, for up to a total of 4 doses, starting with UbiLT3. At C4D1 until C6D1, vaccine will be given q4w. It will be given again at C9D1 and C12D1 (See Figure 3.1.6-1)							

Abbreviations: ADA = anti-drug antibody; AFP = alpha fetal protein; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BMS = Bristol-Myers Squibb; C = Cycle; CBC = complete blood count; CEA = carcinoembryonic antigen; CR = complete response; CRC = colorectal cancer; D = Day; EOT = end of treatment; LFT = liver function test; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IRT = Interactive Response Technology; LFT = liver function test; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PR = partial response; PSA = Prostate-Specific Antigen; RNA = ribonucleic acid; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; VS = vital signs.

[a] EOT is defined as the visit where the decision is made to discontinue the subject from treatment.

[b] For subjects who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C26D28) and the start of the Week 1 Safety Follow-up visit.

[c] For subjects who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated and will be considered the start of the Week 1 Safety Follow-up visit.

[d] Subjects will have procedures listed in this table completed at all cycles. One cycle = 4 weeks.

[e] For DPV-001, on C1D1, vital signs will be collected at pre-dose and then every 15 minutes (± 5 minutes) until 1 hour post dose; on C1D8 and beyond, vital signs will be obtained at pre-dose and then every 15 minutes (± 5 minutes) until 30 minutes post dose. For nivolumab, vital signs will be collected before the infusion and then every 30 minutes (± 10 minutes) until the start of the next study drug infusion or per institution guidelines. The 30-minute post nivolumab infusion vital sign may correspond to the pre-infusion BMS-986178 vital sign. In the event the next study drug administration is delayed, nivolumab vital signs will be obtained until 60 minutes after completion of the infusion. For BMS-986178, on C1D1 and C2D1, vital signs will be obtained before the infusion and then every 30 minutes until 4 hours post infusion; on C3D1 and beyond, vital signs will be taken every 15 minutes (± 5 minutes) until 60 minutes post infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.

[f] Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If the pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue and immediately notify the BMS Medical Monitor/designee per Section 6.4.

Table 5.1-9: Follow-up Procedural Outline Parts 1 - 9 (CA012004)

Procedure	Safety Follow-up			Notes
	FU 1 30 Days[a] (± 7 days)	FU 2 60 Days (± 7 days)	FU 3 100 Days (± 10 days)	
Safety Assessments				
Physical Examination (PE)	X	X	X	
Vital Signs	X	X	X	Includes body temperature, seated blood pressure, and heart rate.
Laboratory Tests				
Chemistry (excluding LFTs)	X	X	X	See Section 5.3.2.
CBC with Differential and Platelets	X	X	X	
LFT Assessment	X	X	X	LFTs will be monitored following the last dose of BMS-986178. Includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated) alkaline phosphatase, and GGT (if ALP increase is clinically significant).
Urinalysis	As clinically indicated. See Section 5.3.2.			
Pregnancy Test	X	X	X	For WOCBP; serum or urine pregnancy test may be performed (clinic urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG). If positive, perform confirmatory testing. If pregnancy is confirmed, immediately notify the BMS Medical Monitor/designee per Section 6.4.
Adverse Event Reporting [redacted]				
Monitor for Non-Serious Adverse Events	X[b]	X[b]	X[c]	Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.
Monitor for Serious Adverse Events and any AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infections	X[b]	X[b]	X[c]	See note in screening procedures (Table 5.1-1). Participants will be followed for all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the particpants is lost to follow-up (as defined in Section 3.6.2), or for suspected cases, until SARS-CoV-2 infection is ruled out.

Table 5.1-9: Follow-up Procedural Outline Parts 1 - 9 (CA012004)

Procedure	Safety Follow-up			Notes
	FU 1 30 Days[a] (± 7 days)	FU 2 60 Days (± 7 days)	FU 3 100 Days (± 10 days)	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sample Collection				
Pharmacokinetic Assessments	X	X	X	See Table 5.5.1-1 (Parts 1 and 2), Table 5.5.1-2 (Part 4), Table 5.5.1-3 (Parts 3 and 5), Table 5.5.1-4 (Part 6), Table 5.5.1-5 (Part 7), Table 5.5.1-6 (Part 8), and Table 5.5.1-7 (Part 9).
Immunogenicity (ADA) Assessments	X	X	X	See Table 5.5.1-1 (Parts 1 and 2), Table 5.5.1-2 (Part 4), Table 5.5.1-3 (Parts 3 and 5), Table 5.5.1-4 (Part 6), Table 5.5.1-5 (Part 7), Table 5.5.1-6 (Part 8), and Table 5.5.1-7 (Part 9).
Efficacy Assessments				
Tumor/Response Assessments			X	Diagnostic imaging by method used at baseline; an unconfirmed PR or unconfirmed CR must be confirmed at least 4 weeks after initial assessment. Assessed by RECIST v1.1; see Appendix 3. Subjects who discontinue study drug must continue to be followed per the Safety Follow-up (approximately 100 days)
Subsequent Treatments (Anti cancer)	X	X	X	Include documentation of subsequent cancer therapy (ie, systemic therapy, tumor-directed surgery, or radiation therarpy).

Abbreviations: ADA = anti-drug antibody; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BMS = Bristol-Myers Squibb; CBC = complete blood count; CR = complete response; EOT = end of treatment; FU = Follow-Up; LFT = liver function test; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; LFT = liver function test; PD = pharmacodynamic; PR = partial response; RO = receptor occupancy; SAE = serious adverse event; SD =stable disease; SOC = standard of care; TCR = T-cell receptor; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; WOCBP = women of child bearing potential.

[a] Follow-up visits at Days 30, 60 (±7 days), and 100 (±10 days) should occur after the last dose or coinciding with the date of discontinuation ±7 days if the date of discontinuation is greater than 30 days after the last dose to monitor for adverse events.

[b] Record at each visit. Collect continuously throughout the treatment period and for a minimum of 100 days following discontinuation of dosing.

[c] Beyond 100 days from the last dose of study therapy, participants will be followed for drug-related AEs/SAEs until resolution, returns to baseline, or is deemed irreversible, or until the participant is lost to follow-up or withdraws study consent.

In the event that multiple procedures are required at a single time point, the following is a list of procedures from highest to lowest priority:

1) PK Sampling
2) Safety (ECG)
3) Safety (clinical laboratories)

5.1.1 Retesting During Screening

Retesting of laboratory parameters and/or other assessments within any single screening will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 5.1-1 may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor (or designee) may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

Testing for asymptomatic SARS-CoV-2 infection by RT-PCR or viral antigen is not required. However, some subjects may develop suspected or confirmed symptomatic SARS-CoV-2 infection, or be discovered to have asymptomatic SARS-CoV-2 infection during the screening period. In such cases, subjects may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting all of the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR or viral antigen test result
- At least 24 hours have passed since last fever without the use of fever-reducing medications
- Acute symptoms (eg, cough, shortness of breath) have resolved
- In the opinion of the investigator, there are no SARS-CoV-2 sequelae that may place the participant at a higher risk of receiving investigational treatment.

5.2 Study Materials

The site will provide all required materials for the tests performed locally (ie, relevant clinical laboratory tests and urine drug screens). The site will have a well-calibrated scale available for recording body weight, a 12-lead ECG machine, and a calibrated sphygmomanometer, a syringe pump, 0.2-µm filter infusion sets, and a thermometer for vital signs assessments. A current and fully stocked advanced cardiac life support cart will be immediately available on the premises. The site will have a refrigerated centrifuge, a monitored and alarmed refrigerator, and freezer (-70°C preferred, -20°C acceptable), as well as containers and dry ice for shipment and storage of blood

samples. The site will provide all materials required for accurate source documentation of study activities and for housing the subjects during the study. The site will source marketed product from a single commercial lot.

BMS will provide a Sponsor-approved protocol and any amendments or administrative letters (if required) and an IB. CRFs (electronic or hard copy) will be provided by BMS. BMS/central laboratory will provide labels and tubes for the collection of blood samples for PK/PD and for genotyping analysis.

5.3 Safety Assessments

AEs will be assessed during the study and for 100 days after the last treatment. AEs will be evaluated according to NCI CTCAE v4.03 and should be followed per requirements in Section 6.1 and Section 6.2. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities and reviewed for potential significance and importance. Subjects should be followed until all treatment-related AEs have recovered to baseline or are deemed irreversible by the investigator.

Protocol-specified assessments are described in Table 5.1-1 (Screening), Table 5.1-2 (On Treatment - Parts 1 and 2), Table 5.1-3 (On Treatment - Parts 3 and 5), Table 5.1-4 (On Treatment - Part 4), Table 5.1-5 (On Treatment - Part 6), Table 5.1-6 (On Treatment - Part 7), Table 5.1-7 (On Treatment - Part 8), Table 5.1-8 (On Treatment - Part 9), and Table 5.1-9 (Follow-up - Parts 1-9).

5.3.1 Imaging Assessment for the Study

1) CT/MRI
   a) Contrast-enhanced CT scans acquired on dedicated CT equipment is preferred for this study. CT with contrast of the chest, abdomen, and pelvis are to be performed for tumor assessments. CT scans should be acquired with 5-mm slices and no intervening gap (contiguous).
      (1) Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen and pelvis may be obtained. MRIs should be acquired with slice thickness of < 5 mm with no gap (contiguous).
      (2) Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.
      (3) Note on the use of the CT component of a positron emission tomography (PET)/CT scanner:

   Combined modality scanning such as with fluorodeoxyglucose (FDG)-PET/CT is increasingly used in clinical care and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low-dose or attenuation-correction CT portions of a combined FDG-PET/CT are of limited use in anatomically based efficacy assessments; it is therefore suggested that they should not be substituted for dedicated diagnostic contrast-enhanced CT scans

for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the FDG-PET/CT can be used for RECIST 1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

2) Brain MRI
   a) MRI of the brain is required at screening if subject is symptomatic or has a history of brain metastasis. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks or sooner, if clinically indicated.
   b) MRI brain scans during on-study treatment and follow-up periods are required **only** if there is a prior history of lesions present at Screening, or as clinically indicated for new signs and symptoms that suggest central nervous system (CNS) involvement.
3) Bone Scan
   a) Bone scans can be used to evaluate metastatic disease.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

5.3.2 Laboratory Test Assessments

Each site's local laboratory will perform the analyses and will provide reference ranges for these tests.

Results of clinical laboratory tests performed on Day -3 and Day 1 must be available prior to dosing.

The following clinical laboratory tests will be performed:

Hematology

Hemoglobin
Hematocrit
Platelet count
Total leukocyte count, including differential

CBC and differential results will be monitored on an ongoing basis and should be sent to the local laboratory data service upon receipt of the results. Others will be sent to the local laboratory data service.

Serum Chemistry

AST
ALT
Amylase
Total bilirubin
Total protein
Albumin
Sodium
Potassium

Direct bilirubin (only as reflex when T bilirubin elevated)
ALP
Lactate dehydrogenase
Lipase
Creatinine
Blood urea nitrogen
Uric acid (at screening only)
Glucose (fasting at screening)
Gamma-glutamyl transferase (only as reflex when ALP increase is clinically significant)
Chloride
Calcium
C-reactive protein
Ferritin
Carbon dioxide
Phosphorus
Magnesium
CrCL(screening only)

Thyroid Laboratories

Thyroid-stimulating hormone (TSH)
Free T3 and free T4 (at screening and reflex when TSH abnormal)

Urinalysis

Protein
Glucose
Blood
Leukocyte esterase
Specific gravity
pH
Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive

Serology

Hepatitis B surface antigen
Serum for hepatitis C antibody(if Hep C Ab is positive reflex to Hep C RNA) or Hep C RNA, HIV-1 and -2 antibody (testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements).

Other Analyses

Pregnancy test (WOCBP only: serum testing at screening and within 24 hours prior to dosing; urine or serum at all other time points).
FSH (screening only for women only)

Tumor Specific Serum Markers

CA125 testing for all subjects with OC

Alpha fetal protein (AFP) testing for all subjects with hepatocellular carcinoma

Carcinoembryonic antigen (CEA) testing for all subjects with CRC

CA19-9 testing for all subjects with pancreatic cancer

Prostate-Specific Antigen test for all subjects with prostate cancer

CA15.3 and CEA for all Part 9 subjects, with TNBC and ER-low positive breast cancer (at baseline, and subsequently if baseline levels are above upper limit of normal).

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 6.3).

5.4 Efficacy Assessments

Disease assessment with CT and/or MRI as appropriate will be performed at baseline and every 8 weeks Parts 1-7, and 9 or every 12 weeks for Part 8 (± 1 week) per RECIST v1.1 (see Appendix 3) until discontinuation of treatment or withdrawal from study. Tumor assessments at other time points may be performed if the investigator is concerned about tumor progression. Assessment of tumor response will be reported by the investigator for appropriate populations of subjects as defined by RECIST v1.1[181] (see Appendix 3) for subjects with advanced solid tumors. The same modality should be used and the same scanner is preferred for all assessments.

Investigators will also report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the CRF based on the investigators' assessment using RECIST criteria. Please refer to Appendix 3 for specifics of RECIST v1.1 criteria to be utilized in this study.

5.4.1 Primary Efficacy Assessment

Not applicable.

5.4.2 Secondary Efficacy Assessments

The efficacy assessments will include ORR (eg, PR and CR) for Parts 1-9; duration of response and progression-free survival rate (PFSR) at time points (eg, 24 weeks) for Parts 1-8, based on assessment of tumor response using RECIST v1.1.

5.4.3 Exploratory Efficacy Assessments

OS data will be collected up to 2 years from the start of study drug treatment for Parts 1-8.

5.5 Pharmacokinetic Assessments

Samples for PK and immunogenicity assessments will be collected for subjects receiving BMS-986178 alone or in combination with nivolumab and/or ipilimumab, as described in Table 5.5.1-1 (Parts 1 and 2), Table 5.5.1-2 (Part 4), Table 5.5.1-3 (Parts 3 and 5), Table 5.5.1-4 (Part 6), Table 5.5.1-5 (Part 7), Table 5.5.1-6 (Part 8), and Table 5.5.1-7 (Part 9). The PK of BMS-986178 will be characterized by NCA method. Immunogenicity samples will be analyzed for anti-BMS-986178 antibodies and/or anti-nivolumab antibodies and/or anti-ipilimumab antibodies by validated immunoassays.

If data permit, the PK parameters might be assessed following Cycle 1 Day 1 and Cycle 9 Day 1 for the q2w dosing regimen in monotherapy or in combination therapy, Cycle 4 Day 1 for the q3w or q6w dosing regimen in combination therapy with ipilimumab and/or nivolumab combination

therapy, Cycle 5 Day 1 for q4w dosing regimen in combination therapy with nivolumab include the following:

Cmax	Maximum observed serum concentration
Tmax	Time of maximum observed concentration
AUC(0-t)	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(TAU)	Area under the concentration-time curve in 1 dosing interval

In addition, the PK parameters listed below may be assessed following dose administration in Cycle 9 Day 1 for the q2w or Cycle 5 Day 1 for q4w dosing regimen in monotherapy or in combination therapy and Cycle 4 Day 1 for the q3w and q6w dosing regimen in combination therapy with ipilimumab and/or nivolumab.

Ctau	The observed concentration at the end of a dosing interval
CLT	Total body clearance
Css-avg	Average concentration over a dosing interval (AUC(TAU)/tau)
AI	Ratio of an exposure measure at steady state (eg, following Cycle 9 Day 1 dose) to that after the first dose (exposure measure includes AUC(TAU), Cmax and Ctau).
T-HALFeff	Effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure (exposure measure includes AUC(TAU), Cmax and Ctau)

The following PK parameter will be reported as a separate listing, summary, and plot:

Ctrough	Trough observed plasma concentrations (this includes predose concentrations (C0) and Ctau)

5.5.1 Pharmacokinetics and Immunogenicity Collection and Processing

Detailed sampling schedules to be followed for the assessment of PK and immunogenicity for BMS-986178 monotherapy or in combination therapy are provided in Table 5.5.1-1 (Parts 1 and 2), Table 5.5.1-2 (Part 4), Table 5.5.1-3 (Parts 3 and 5), Table 5.5.1-4 (Part 6), Table 5.5.1-5 (Part 7), Table 5.5.1-6 (Part 8) and Table 5.5.1-7 (Part 9). However, if there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit).

All predose samples should be taken within 30 minutes before the start of any dose infusion. All postdose PK sampling time points are relative to the start of BMS-986178 administration. End-of-infusion samples should be taken just prior to the end of infusion (EOI; preferably within 2 minutes). Further details of sample collection, processing, and shipment will be provided in the laboratory procedure manual. On-treatment PK samples are intended to be drawn relative to actual dosing days; if a dose occurs on a different day within the cycle due to delays or minor schedule adjustments, PK samples should be adjusted accordingly.

Table 5.5.1-1: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 Monotherapy or in Combination Therapy - Parts 1 and 2 (CA012004 - q2w Dosing)

Study Day of Sample Collection (1 Cycle = 2 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	BMS-986178 PK Sample (All Subjects)	Nivolumab PK Sample (Part 2)	BMS-986178 ADA Sample (All Subjects)	Nivolumab ADA Sample (Part 2)
C1D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
		04:00	X			
C1D2		24:00	X			
C1D4[c]		72:00	X			
C1D8[d]		168:00	X			
C2D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
C3D1	Predose[a]	00:00[a]	X	X	X	X
C4D1	Predose[a]	00:00[a]	X	X		
End of Treatment						
Unscheduled[e]			X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = Cycle; D = Day; EOI = end of infusion.

[a] Predose: All predose samples for combinations should be collected prior to the start of the first infusion.

[b] EOI samples for both nivolumab and BMS-986178 should be collected at the end of the BMS-986178 infusion. The EOI sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] D4 sample may be taken during D3 to D5 of a cycle.

[d] D8 sample may be taken during D7 to D9 of a cycle.

[e] Unscheduled: If there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit).

Table 5.5.1-2: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 in Combination Therapy - Part 4 (CA012004 - q4w Dosing)

Study Day of Sample Collection (1 Cycle = 4 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	BMS-986178 PK Sample	Nivolumab PK Sample	BMS-986178 ADA Sample	Nivolumab ADA Sample
C1D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
		04:00	X			
C1D2		24:00	X			
C1D4[c]		72:00	X			
C1D8[d]		168:00	X			
C1D15[e]		336:00	X			
C2D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
C3D1	Predose[a]	00:00[a]	X	X	X	X
C4D1	Predose[a]	00:00[a]	X	X	X	X
End of Treatment						
Unscheduled[f]			X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = Cycle; D = Day; EOI = end of infusion.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Predose: All predose samples for combinations should be collected prior to the start of the first infusion.

[b] EOI samples for both nivolumab and BMS-986178 should be collected at the end of the BMS-986178 infusion. The EOI sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] D4 sample may be taken during D3 to D5 of a cycle.

[d] D8 sample may be taken during D7 to D9 of a cycle.

[e] D15 sample may be taken during D12 to D18 of a cycle.

[f] Unscheduled: If there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit).

Table 5.5.1-3: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 in Combination with Ipilimumab - Parts 3 and 5 (CA012004 - q3w Dosing)

Study Day of Sample Collection (1 Cycle = 3 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	BMS-986178 PK Sample	Ipilimumab PK Sample	BMS-986178 ADA Sample	Ipilimumab ADA Sample
C1D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
		04:00	X			
C1D2		24:00	X			
C1D4[c]		72:00	X			
C1D8[d]		168:00	X			
C1D15[d]		336:00	X			
C2D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
C3D1	Predose[a]	00:00[a]	X	X	X	X
C4D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
		04:00	X			
C4D2		24:00	X			
C4D4[c]		72:00	X			
C4D8[d]		168:00	X			
C4D15[d]		336:00	X			
End of Treatment						
Unscheduled[e]			X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = Cycle; D = Day; EOI = end of infusion.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Predose: All predose samples for combinations should be collected prior to the start of the first infusion.

[b] EOI samples for both ipilimumab and BMS-986178 should be collected at the end of the BMS-986178 infusion. The EOI sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] D4 sample may be taken during D3 to D5 of a cycle.

[d] D8 sample may be taken during D7 to D9 of a cycle; Day 15 sample may be taken during D13 to D17 of a cycle.

[e] Unscheduled: If there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled isit).

Table 5.5.1-4: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 in Combination - Part 6 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with RCC)

Study Day of Sample Collection (Cycle = 3 Weeks for C1 - C4 Cycle = 4 Weeks for C5 and Beyond)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	BMS-986178 PK Sample	Nivolumab PK Sample	Ipilimumab PK Sample	BMS-986178 ADA Sample	Nivolumab ADA Sample	Ipilimumab ADA Sample
C1D1	Predose[a]	00:00[a]	X	X	X	X	X	X
	EOI[b]	00:30[b]	X	X	X			
		04:00	X					
C1D2		24:00	X					
C1D4[c]		72:00	X					
C1D8[d]		168:00	X					
C1D15[e]		336:00	X					
C2D1	Predose[a]	00:00[a]	X	X	X	X	X	X
	EOI[b]	00:30[b]	X	X	X			
C3D1	Predose[a]	00:00[a]	X	X	X	X	X	X
C4D1	Predose[a]	00:00[a]	X	X	X	X	X	X
	EOI[b]	00:30[b]	X	X	X			
		04:00	X					
C4D2		24:00	X					
C4D4[c]		72:00	X					

Table 5.5.1-4: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 in Combination - Part 6 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with RCC)

Study Day of Sample Collection (Cycle = 3 Weeks for C1 - C4 Cycle = 4 Weeks for C5 and Beyond)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	BMS-986178 PK Sample	Nivolumab PK Sample	Ipilimumab PK Sample	BMS-986178 ADA Sample	Nivolumab ADA Sample	Ipilimumab ADA Sample
C4D8[d]		168:00	X					
C4D15[e]		336:00	X					
End of Treatment								
Unscheduled[f]			X	X	X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = Cycle; D = Day; EOI = end of infusion.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Predose: All predose samples for combinations should be collected prior to the start of the first infusion.

[b] EOI samples for ipilimumab, nivolumab, and BMS-986178 should be collected at the end of the BMS-986178 infusion. The EOI sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] D4 sample may be taken during D3 to D5 of a cycle.

[d] D8 sample may be taken during D7 to D9 of a cycle.

[e] D15 sample may be taken during D13 to D17 of a cycle.

[f] Unscheduled: If there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit).

Table 5.5.1-5: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 in Combination - Part 7 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with NSCLC)

Study Day of Sample Collection (1 Cycle = 6 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	BMS-986178 PK Sample	Nivolumab PK Sample	Ipilimumab PK Sample	BMS-986178 ADA Sample	Nivolumab ADA Sample	Ipilimumab ADA Sample
C1D1	Predose[a]	00:00[a]	X	X	X	X	X	X
	EOI[b]	00:30[b]	X	X	X			
		04:00	X					
C1D2		24:00	X					
C1D4[c]		72:00	X					
C1D8[d]		168:00	X					
C1D15[e]	Predose[a]	00:00[a]	X	X				
C1D29[f]	Predose[a]	00:00[a]	X	X				
C2D1	Predose[a]	00:00[a]	X	X	X	X	X	X
	EOI[b]	00:30[b]	X	X	X			
C3D1	Predose[a]	00:00[a]	X	X	X	X	X	X
C4D1	Predose[a]	00:00[a]	X	X	X	X	X	X
	EOI[b]	00:30[b]	X	X	X			
		04:00	X					
C4D2		24:00	X					
C4D4[c]		72:00	X					

Table 5.5.1-5: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 in Combination - Part 7 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with NSCLC)

Study Day of Sample Collection (1 Cycle = 6 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	BMS-986178 PK Sample	Nivolumab PK Sample	Ipilimumab PK Sample	BMS-986178 ADA Sample	Nivolumab ADA Sample	Ipilimumab ADA Sample
C4D8[d]		168:00	X					
C4D15[e]	Predose[a]	00:00[a]	X	X				
C4D29[f]	Predose[a]	00:00[a]	X	X				
End of Treatment								
Unscheduled[g]			X	X	X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = Cycle; D = Day; EOI = end of infusion.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Predose: All predose samples for combinations should be collected prior to the start of the first infusion.

[b] EOI samples for ipilimumab, nivolumab, and BMS-986178 should be collected at the end of the BMS-986178 infusion. The EOI sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly

[c] D4 sample may be taken during D3 to D5 of a cycle.

[d] D8 sample may be taken during D7 to D9 of a cycle.

[e] D15 sample may be taken during D13 to D17 of a cycle.

[f] D29 sample may be taken during D26 to D30 of a cycle.

[g] Unscheduled: If there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit).

Table 5.5.1-6: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 in Combination - Part 8 (CA012004 - q12w Dosing)

Study Day of Sample Collection (1 Cycle = 12 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	BMS-986178 PK Sample (Cohort 1-3)	Nivolumab PK Sample	BMS-986178 ADA Sample (Cohort 1-3)	Nivolumab ADA Sample
C1D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
		04:00	X			
C1D8[c]		168:00	X	X		
C1D15[d]		336:00	X	X		
C1D29[e]		696:00	X	X	X	X
C2D1	Predose[a]	00:00[a]	X	X	X	X
	EOI[b]	00:30[b]	X	X		
		04:00	X			
C2D8[c]		168:00	X	X		
C2D15[d]		336:00	X			
C2D29[e]		696:00	X	X		
C3D1	Predose[a]	00:00[a]	X	X	X	X
End of Treatment						
Unscheduled[f]			X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = Cycle; D = Day; EOI = end of infusion.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Predose: All predose samples for combinations should be collected prior to the start of the first infusion.

[b] EOI samples for both nivolumab and BMS-986178 should be collected at the end of the BMS-986178 infusion. The EOI sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] D8 sample may be taken during D7 to D9 of a cycle.

[d] D15 sample may be taken during D12 to D18 of a cycle.

[e] D29 sample may be taken prior nivolumab infusion.

[f] Unscheduled: If there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit).

Table 5.5.1-7: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986178 in Combination Therapy - Part 9 (CA012004 - q4w Dosing)

Study Day of Sample Collection (1 Cycle = 4 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion in Cohort 1 or Relative to Start of Nivolumab in Cohort 2) Hour: Min	BMS-986178 PK Sample (Cohort 1 only)	Nivolumab PK Sample	BMS-986178 ADA Sample (Cohort 1 only)	Nivolumab ADA Sample
C1D1	Predose[a]	00:00	X		X	
C1D8[b]		168:00[d]	X			
C1D15[c]		336:00[d]	X	X		X
C2D1	Predose[a]	00:00[a]	X	X	X	X
C3D1	Predose[a]	00:00[a]	X	X		
C5D1	Predose[a]	00:00[a]	X	X	X	X
C6D1	Predose[a]	00:00[a]	X	X	X	X
End of Treatment						
EOT	EOT		X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = Cycle; D = Day; EOT = end of treatment; FU = Follow-Up.

[a] Predose: All predose samples for combinations should be collected prior to the start of the first infusion

[b] D8 sample may be taken during D7 to D9 of a cycle.

[c] D15 sample may be taken during D12 to D18 of a cycle.

[d] Relative to start of DPV-001 administration on C1D1 in Cohort 2

5.5.1.1 Pharmacokinetic and Immunogenicity Sample Analyses

The serum samples will be analyzed for drug (BMS-986178 and/or nivolumab and/or ipilimumab) and ADA (anti-BMS-986178 antibodies and/or anti-nivolumab antibodies and/or anti-ipilimumab antibodies) by validated immunoassays. In addition, selected serum samples may be analyzed by an exploratory method that measures BMS-986178, nivolumab, and ipilimumab; or detect ADAs for technology exploration purposes; exploratory results will not be reported. Serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity-related AE).

5.5.2 Labeling and Shipping of Biological Samples

Detailed instructions for the PK blood collection, labeling, processing, storage, and shipping will be provided to the site in the laboratory procedure manual.

5.6 Biomarker Assessments

To assess the PD effects of BMS-986178 as well as receptor occupancy (RO) in relation to dose and PK, whole blood samples (blood PD and blood RO) will be collected at the times indicated in Table 5.6-1 (Parts 1 and 2), Table 5.6-2 (Parts 3, 5, and 6), Table 5.6-3 (Part 4), Table 5.6-4 (Part 7), Table 5.6-5 (Part 8), and Table 5.6-6 (Part 9). The sample testing plans associated with each are described in Section 5.7. Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided in a separate laboratory procedure manual.

Blood samples for PD assessment will be analyzed by cytometry to determine baseline and serial on-treatment alterations in composition and/or activation status of lymphocyte subsets. Lymphocyte subsets to be assayed may include, but are not limited to, CD8+ and CD4+ T-cell subsets (activated; effector/memory; regulatory) and populations of those cells as defined by the expression of proliferation, activation, exhaustion, or signaling markers such as KI67, HLA-DR, PD-1, etc. Treatment-induced alterations in blood lymphocyte populations will be analyzed in relation to both dose and blood concentrations of BMS-986178.

Receptor occupancy of OX40 by BMS-986178 (RO) on peripheral blood mononuclear cells (PBMCs) may also be determined by flow cytometry. RO will be analyzed in relation to PK and PD effects. Samples will be collected to determine RO from subjects in Part 1A and 1B in this study. For combination cohorts, a blood tube will also be collected for exploratory purposes to measure pharmacodynamic endpoints including, but not limited to RO.

Fecal microbiome will be collected prior to treatment for subjects in Part 9.

Table 5.6-1: Pharmacodynamic and Exploratory Biomarker Sampling Schedule for BMS-986178 Monotherapy and Combination Therapy - Parts 1 and 2 (CA012004 - q2w Dosing)

Study Day of Sample Collection (1 Cycle = 2 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	Blood RNA, Blood RO[a]	Blood PD	PBMC, Blood Multiparameter Flow, Serum Factors, Plasma[b]	Tumor Biopsy[c] Section 5.6	Blood Genotype, Blood TCR[d]	Archived Tumor[e]
Screening				X		X	X	X
C1D1	Predose[f]	00:00	X	X	X			
C1D2		24:00			X			
C1D8[g]		168:00	X	X	X			
C2D1	Predose[f]	00:00	X	X	X	X[h]		
C3D1	Predose[f]	00:00		X	X		X	
EOT/Unscheduled/ Progression	EOT			X	X	X	X	

Abbreviations: C = Cycle; D = Day; EOT = end of treatment; FFPE = formalin-fixed, paraffin-embedded; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; RNA = ribonucleic acid; RO = receptor occupancy; TCR = T cell receptor.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Separate samples will be collected for blood RNA and blood RO assessments. Blood RNA samples will be collected from all subjects. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[b] Separate samples will be collected for PBMC, blood multiparameter flow, serum factors, and plasma assessments. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[c] Mandatory predose and on-treatment biopsies for all subjects. Additional subjects may be added in the event that some subjects do not have obtainable tumor at the on-treatment time point. Subjects obtaining biopsies should have adequate tissue collected as outlined in the laboratory manual. Additional optional biopsies may be collected at EOT, time of disease progression, or during another clinically meaningful event (eg, response or adverse event).

[d] Blood genotype sample to be collected at screening only

[e] All subjects may provide an archived tumor specimen. Archival FFPE block or a minimum of 15 slides is required; 25 slides are preferred. See laboratory manual.

[f] Predose: All predose samples for combinations should be taken prior to the start of the first infusion.

[g] D8 sample may be taken during D7 to D9 of a cycle.

[h] C2D1 fresh tumor biopsy may be taken during C1D12-C2D4.

Table 5.6-2: Pharmacodynamic and Exploratory Biomarker Sampling Schedule for BMS-986178 Combination Therapy - Parts 3, 5, and 6 (CA012004)

Study Day of Sample Collection (Cycle = 3 Weeks for C1 C8 for Parts 3 and 5) (Cycle = 3 Weeks for C1 C4 Cycle = 4 Weeks for C5 and Beyond for Part 6)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	Blood RO, Blood RNA[a]	Blood PD	PBMC, Blood Multiparameter Flow, Serum Factors, Plasma[b]	Tumor Biopsy[c]	Blood Genotype, Blood TCR[d]	Archived Tumor[e]
Screening				X		X	X	X
C1D1	Predose[f]	00:00	X	X	X			
C1D2		24:00			X			
C1D8[g]		168:00	X	X	X			
C1D15[h]		336:00	X	X	X	X		
C2D1	Predose[f]	00:00	X	X	X		X	
C2D8								
C3D1	Predose[f]	00:00	X	X	X			
C4D1	Predose[f]	00:00	X	X	X		X	
EOT/Unscheduled/Progression	EOT			X	X	X	X	

Abbreviations: C = Cycle; D = Day; EOT = end of treatment; FFPE = formalin-fixed, paraffin-embedded; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; RO=Receptor Occupancy RNA = ribonucleic acid; TCR = T cell receptor.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Separate samples will be collected for blood RNA and blood RO assessments from all subjects. Detailed instructions for the collection, processing, and shipping of samples will be provided in the laboratory procedure manual.

[b] Separate samples will be collected for PBMC, blood multiparameter flow, serum factors, and plasma assessments. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[c] Mandatory predose and on-treatment biopsies for all subjects. Additional subjects may be added in the event that some subjects do not have obtainable tumor at the on-treatment time point. Subjects obtaining biopsies should have adequate tissue collected as outlined in the laboratory manual. Additional optional biopsies may be collected at EOT, time of disease progression, or during another clinically meaningful event (eg, response or adverse event).

[d] Blood genotype sample to be collected at screening only.

[e] All subjects may provide an archived tumor specimen. Archival FFPE block or a minimum of 15 slides is required; 25 slides are preferred. See laboratory manual.

[f] Predose: All predose samples for combinations should be taken prior to the start of the first infusion.

[g] D8 sample may be taken during D7 to D9 of a cycle.

[h] D15 sample may be taken during D13 to D17 of a cycle.

Table 5.6-3: Pharmacodynamic and Exploratory Biomarker Sampling Schedule for BMS-986178 Combination Therapy - Part 4 (CA012004 - q4w Dosing)

Study Day of Sample Collection (1 Cycle = 4 Weeks	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	Blood RNA, Blood RO[a]	Blood PD	PBMC, Blood Multiparameter Flow, Serum Factors, Plasma[b]	Tumor Biopsy[c]	Blood Genotype, Blood TCR[d]	Archived Tumor[e]
Screening				X		X	X	X
C1D1	Predose[f]	00:00	X	X	X			
C1D2		24:00			X			
C1D8[g]		168:00	X	X	X			
C1D15[h]		336:00	X	X	X	X		
C2D1	Predose[f]	00:00	X	X	X		X	
C3D1	Predose[f]	00:00	X	X	X		X	
EOT/Unscheduled/ Progression	EOT			X	X	X	X	

Abbreviations: C = Cycle; D = Day; EOT = end of treatment; FFPE = formalin-fixed, paraffin-embedded; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; RNA = ribonucleic acid; RO = receptor occupancy; TCR = T cell receptor.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Separate samples will be collected for blood RNA and blood RO assessments from all subjects. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[b] Separate samples will be collected for PBMC, blood multiparameter flow, serum factors, and plasma assessments. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[c] Mandatory predose and on-treatment biopsies for all subjects. Additional subjects may be added in the event that some subjects do not have obtainable tumor at the on-treatment time point.. Subjects obtaining biopsies should have adequate tissue collected as outlined in the laboratory manual. Additional optional biopsies may be collected at EOT, time of disease progression, or during another clinically meaningful event (eg, response or adverse event).

[d] Blood genotype sample to be collected at screening only.

[e] All subjects may provide an archived tumor specimen. Archival FFPE block or a minimum of 15 slides is required; 25 slides are preferred. See laboratory manual

[f] Predose: All predose samples for combinations should be taken prior to the start of the first infusion.

[g] D8 sample may be taken during D7 to D9 of a cycle.

[h] D15 sample may be taken during D12 to D18 of a cycle.

Table 5.6-4: Pharmacodynamic and Exploratory Biomarker Sampling Schedule for BMS-986178 Combination Therapy - Part 7 (CA012004; BMS-986178 with Nivolumab and Ipilimumab in Subjects with NSCLC)

Study Day of Sample Collection (1 Cycle = 6 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	Blood RNA, Blood RO[a]	Blood PD	PBMC, Blood Multiparameter Flow, Serum Factors, Plasma[b]	Tumor Biopsy[c] Section 5.6	Blood Genotype,[d] Blood TCR	Archived Tumor[e]
Screening				X		X	X	X
C1D1	Predose[f]	00:00	X	X	X			
C1D2		24:00			X			
C1D8[g]		168:00	X	X	X			
C1D15[h]	Predose[f]	00:00	X	X	X	X		
C1D29[i]	Predose[f]	00:00	X	X	X			
C2D1	Predose[f]	00:00	X	X	X		X	
C3D1	Predose[f]	00:00		X	X		X	
EOT/Unscheduled/ Progression	EOT			X	X	X	X	

Abbreviations: C = Cycle; D = Day; EOT = end of treatment; FFPE = formalin-fixed, paraffin-embedded; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; RNA = ribonucleic acid; RO = receptor occupancy; TCR = T cell receptor.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Separate samples will be collected for blood RNA and blood RO assessments. Blood RNA samples will be collected from all subjects. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[b] Separate samples will be collected for PBMC, blood multiparameter flow, serum factors, and plasma assessments. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[c] Mandatory predose and on-treatment biopsies for all subjects. Additional subjects may be added in the event that some subjects do not have obtainable tumor at the on-treatment time point. Subjects obtaining biopsies should have adequate tissue collected as outlined in the laboratory manual. Additional optional biopsies may be collected at EOT, time of disease progression, or during another clinically meaningful event (eg, response or adverse event).

[d] Blood genotype sample to be collected at screening only.

[e] All subjects may provide an archived tumor specimen. Archival FFPE block or a minimum of 15 slides is required; 25 slides are preferred. See laboratory manual.

[f] Predose: All predose samples for combinations should be taken prior to the start of the first infusion.

[g] D8 sample may be taken during D7 to D9 of a cycle.

[h] D15 sample may be taken during D13 to D17 of a cycle.

[i] D29 sample may be taken during D26 to D30 of a cycle.

Table 5.6-5: Pharmacodynamic and Exploratory Biomarker Sampling Schedule for BMS-986178 Combination Therapy - Part 8 (CA012004 - q12w Dosing

Study Day of Sample Collection (1 Cycle = 12 Weeks)	Event	Time (Relative to start of BMS-986178 Infusion) Hour: Min	Blood RNA, Blood RO[a]	Blood PD	PBMC, Blood Multiparameter Flow, Serum Factors, Plasma[b]	Plasma for ctDNA[j]	Tumor Biopsy[c], Section 5.6	Blood Genotype, Blood TCR[d]	Archived Tumor[e]
Screening				X			X	X	X
C1D1	Predose[f]	00:00	X	X	X	X			
C1D8[g]		168:00	X	X	X				
C1D15[h]		336:00	X	X	X	X	X		
C1D29[i]		672:00	X	X	X	X			
C1D78		1848:00[k]	X	X	X		X		
C2D1	Predose[f]	00:00	X	X	X	X		X	
C2D8[g]		168:00	X	X	X				
C2D15[h]		336:00	X	X	X	X			
C2D29[i]		672:00	X	X	X	X			
C3D1	Predose[f]	00:00	X	X	X	X		X	
C3D8[g]		168:00	X	X	X				
EOT/Unscheduled/ Progression	EOT		X	X	X	X	X	X	

Abbreviations: C = Cycle; D = Day; EOT = end of treatment; FFPE = formalin-fixed, paraffin-embedded; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; RNA = ribonucleic acid; RO = receptor occupancy; TCR = T-cell receptor.

Note: The time recorded is relative to BMS-986178 infusion.

[a] Separate samples will be collected for blood RNA and blood RO assessments. Blood RNA samples will be collected from all subjects. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[b] Separate samples will be collected for PBMC, blood multiparameter flow, serum factors, and plasma assessments. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[c] Mandatory predose and on-treatment biopsies for all subjects. Additional subjects may be added in the event that some subjects do not have obtainable tumor at the on-treatment time point. Subjects obtaining biopsies should have adequate tissue collected as outlined in the laboratory manual. Additional optional biopsies may be collected at EOT, time of disease progression, or during another clinically meaningful event (eg, response or adverse event).

[d] Blood genotype sample to be collected at screening only.

[e] All subjects may provide an archived tumor specimen. Archival FFPE block or a minimum of 15 slides is required; 25 slides are preferred. See laboratory manual.

[f] Predose: All predose samples for combinations should be taken prior to the start of the first infusion.

[g] D8 sample may be taken during D7 to D9 of a cycle.

[h] D15 sample may be taken during D13 to D17 of a cycle.

[i] D29 sample may be taken during D26 to D30 of a cycle.

[j] Blood samples to be collected in 2x 9ml Streck tubes.

[k] C1D78 sample may be taken during D71 to D85.

Table 5.6-6: Pharmacodynamic and Exploratory Biomarker Sampling Schedule for BMS-986178 Combination Therapy - Part 9 (CA012004 - q4w Dosing)

Study Day of Sample Collection (1 Cycle = 4 Weeks)	Event	Time (Relative to Start of BMS-986178 Infusion in Cohort 1 or Relative to Start of Nivolumab in Cohort 2) Hour: Min	Blood RNA[a]	Blood PD	PBMC, Blood Multiparameter Flow, Serum Factors, Plasma[b]	Tumor Biopsy[c] Section 5.6	Blood Genotype, Blood TCR[d]	Archived Tumor[e]	Fecal Micro-biome
Screening			X	X	X[i]	X	X	X	X
Day -3	Predose[f]		X		X[i]				
C1D1	Predose[f]	00:00	X	X	X				
C1D2			X	X	X[i]				
C1D8[g]		168:00[j]		X	X				
C1D15[h]		336:00[j]		X	X				
C2D1	Predose[f]	00:00	X	X	X	X			
C2D15[h]		336:00		X	X				
C3D1	Predose[f]	00:00	X	X	X				
C4- C6D1[f]			X	X	X[i]				
EOT/Unscheduled/ Progression	EOT		X	X	X				

Abbreviations: C = Cycle; D = Day; EOT = end of treatment; FFPE = formalin-fixed, paraffin-embedded; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; RNA = ribonucleic acid; TCR = T-cell receptor.

[a] Blood RNA samples will be collected from all subjects. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual

[b] Separate samples will be collected for PBMC, blood multiparameter flow, serum factors, and plasma assessments. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the laboratory procedure manual.

[c] Mandatory predose and on-treatment biopsies for all subjects. Additional subjects may be added in the event that some subjects do not have obtainable tumor at the on-treatment time point. Subjects obtaining biopsies should have adequate tissue collected as outlined in the laboratory manual. Additional optional biopsies may be collected at EOT, time of disease progression, or during another clinically meaningful event (eg, response or adverse event).

[d] Blood genotype sample to be collected at screening only.

[e] All subjects may provide an archived tumor specimen. Archival FFPE block or a minimum of 15 slides is required; 25 slides are preferred. See laboratory manual.

[f] Predose: All predose samples for combinations should be taken prior to the start of the first infusion.

[g] D8 sample may be taken during D7 to D9 of a cycle.

[h] D15 sample may be taken during D12 to D18 of a cycle.

[i] Serum and PBMC sample only.

[j] Relative to start of DPV-001 administration on C1D1 in Cohort 2.

[redacted]

5.8 Outcomes Research Assessments

Not applicable.

[redacted]

5.10 Additional Research Collection

Additional research collections and retention are mandatory for all subjects, except where prohibited by local laws or regulations.

This protocol will include residual samples for additional research (AR).

This collection for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and the advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

Sample Collection and Storage

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

- Additionally, residual blood (or blood derivatives such as serum, plasma, PBMCs and extracted RNA/DNA) or tumor tissue (archival or fresh biopsy and extracted RNA/DNA) (see Table 5.10-1) will also be retained for additional research purposes.
- Samples will be securely stored by the BMS Biorepository in New Jersey or at a BMS approved third party storage management facility.
- Samples will be stored in a coded fashion; and no researcher will have access to the key, which is securely held at the clinical site, so that there is no direct ability for a researcher to connect a sample to a specific individual.

- Additional research samples will be retained for 15 years or the maximum allowed by applicable law. No additional sampling is required for residual collections.

Further details of sample collection and processing will be provided to the site in the procedure manual.

Table 5.10-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time Points for which residual samples will be retained
PK	All
Archived Tumor Block or Slides	Pre-treatment
Fresh Tumor Biopsy	Pre-treatment, on-treatment and/or unscheduled/EOT
PBMC's	All
Serum	All
Plasma	All
Blood RNA	All
Blood Genotype/Blood TCR	All

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all AE. The causal relationship can be one of the following:

Related: There is no clear alternative cause for the AE that can be identified other than study treatment (e.g. disease progression, environmental causes, unrelated trauma).

Not related: There is a clear alternative cause identified for the AE other than study treatment.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

Immune-mediated adverse events are AEs consistent with immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. Immune-mediated AEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity.

Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

6.1 Serious Adverse Events

An ***SAE*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (See Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)

- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

Participants will be followed for all SAEs and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 3.6.2) or for suspected cases, until SARS-CoV-2 infection is ruled out.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS or designee within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the electronic case report form (eCRF). The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission,

paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious AE*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug until 100 days after discontinuation of dosing. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (electronic) as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 1 year after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

The investigator must immediately notify the BMS Medical Monitor or designee of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome, and where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1for reporting details.).

6.6 Potential Drug-Induced Liver Injury

Specific criteria for identifying pDILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a pDILI event. All occurrences of pDILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

pDILI is defined as:

1) Aminotransaminases (AT) (ALT or AST) elevation > 3 times ULN
   AND
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum ALP),
   AND
3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a pDILI event. All occurrences of pDILIs meeting the defined criteria must be reported as SAEs (see Section 6.1.1 for reporting details).

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, ECG, x-ray filming, or any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

8.1.1 Dose Escalation

As a Phase 1 dose escalation trial, the sample size for each dose escalation cohort depends on observed toxicity and posterior inference. Approximately 30 subjects are expected to be treated during each dose escalation part (BMS-986178 monotherapy [Part 1A], BMS-986178 in combination with nivolumab [Part 2A], and BMS-986178 in combination with ipilimumab [Part 3A]) for a combined total of approximately 90 subjects in Parts 1A, 2A and 3A. Initially, approximately 3 subjects will be treated at the starting dose levels of BMS-986178 or BMS-986178 in combination with nivolumab or ipilimumab. Additional cohorts of approximately 3 evaluable subjects will be treated at recommended dose levels per BLRM (-Copula) recommendations during the dose escalation phase. At least 6 DLT-evaluable subjects will be treated at the MTD. At most, 12 DLT-evaluable subjects will be treated at each dose level. This limit is set to avoid instances in which the model could recommend adding subjects indefinitely to a specific dose level due to uncertainty in the tolerability profile. Escalation by more than 1 dose level (dose skipping) is not permitted.

As in any dose escalation study, the exact number of subjects in the dose escalation cannot be predicted. However, different estimates with the pre-specified parameters of the dose escalation design under various scenarios are provided (see Appendix 1). A maximum of 30 subjects is pre-specified as one of the simulation parameters (assuming approximately 6 subjects per dose level). The simulation provided in Appendix 1 uses combination therapy as an illustration (containing 5 dose levels for BMS-986178 and a fixed dose level for nivolumab [240 mg]). The simulation estimated a total of 15 to 21 subjects on average under different scenarios. Note the following difference between simulation setting and the conduct of the actual trial: 1) dose skipping is allowed in the simulation setting whereas in the actual clinical trial, dose skipping is not permitted, 2) the clinical team can override BLRM (-Copula) dose recommendation based on the totality of data (clinical safety data along with available PK and PD data). Based on these factors, there may be more subjects in the dose escalation phase than the number estimated in the

simulation. For planning purposes, it is assumed that approximately 30 subjects may be treated in each dose escalation part.

8.1.2 Cohort Expansion

The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and PD information regarding BMS-986178 alone or in combination with nivolumab and/or ipilimumab.

In general, the estimated sample size for Parts 2B, 2C, 2D, 3B, 6B, and 7B in expansion phase is guided by Simon 2-stage design, which is based on target response rates (target ORR) and the ability to identify a signal for such clinical response that is above the SOC (historical ORR). Enrollment of subjects at the end of Stage 1 will continue while the initial efficacy evaluation is ongoing. Decisions regarding continuing or not continuing enrollment of a specific arm will be based on a combination of model guidance, clinical judgment on the totality of data (clinical safety, PK, PD, and efficacy), and communication between the Sponsor and investigators. Parts 2E and 3C include tumors from dose escalation for signal seeking. Due to the heterogeneity of response rates of the mixed tumors, approximately 40 subjects is assigned for each part (Part 2E and Part 3C). It is not the intent of the study to use Simon 2-stage design for formal hypothesis testing for the following reasons:

- At an early stage, the Sponsor would like to explore primary anti-tumor activity as a proof of confidence. According to the exploratory nature of an early phase design, the sample size is not large enough to clearly define the patient population. Meanwhile, there are no control arms planned as a comparison.
- In immuno-oncology, it is known that response rate alone does not reflect all potential clinical benefits. Factors such as duration of response, the depth of response, and delayed response could become evident as potential benefits according to the nature of immunotherapy.
- Safety is still the primary objective of the study, and if there is evidence of accumulated toxicity for a dose cohort, the cohort may be discontinued.

The Simon 2-stage design will be used as a guide for the disease-restricted expansion cohorts in Parts 2B, 2C, 2D, 3B, 6B, and 7B.[175,177] The total sample size for each expansion cohort will be calculated to provide a reasonable false-positive rate (FPR) and false-negative rate (FNR) based on assumptions of true (target) and historic ORR for each indication. The sample size and operating characteristics of the Simon 2-stage design are provided in Table 8.1.2-1, although this is not used for hypothesis testing. Approximately 12 subjects for CRC and OCs, 10 subjects for BC, 17 subjects for cervical cancer, and 28 subjects for RCC and NSCLC will be treated in Stage 1 for an initial evaluation of efficacy.

This will inform potential early decisions and guide planning/operations or early termination after taking into consideration additional data, (eg, duration of response and/or SD and safety). If the true response rate is 10% for CRC and OC, the study has a 66% probability of early termination of the cohort. If the true response rate is 25% for BC, the study has a 53% probability of early termination of the cohort. If the true response rate is 20% for cervical cancer, the study has a 55%

probability of early termination of the cohort. If the true response rate is 40% for RCC and NSCLC, the study has a 55% probability of early termination of the cohorts.

For an expansion cohort of 35 subjects in CRC and OC and the assumed true response rate of 30%, there is a 94% chance of observing at least 7 responses (in other words, the FNR is 6%). If the true response rate is only 10% rather than 30%, then there is a 6% chance that there will be at least 7 responses in 35 subjects (in other words, FPR is 6%). Also, if 7 responses are observed (eg, 20% observed response rate), the lower bound of the 80% CI for the ORR is 11% (higher than historical ORR of 10%). The CI is calculated using Clopper-Pearson method.

For an expansion cohort of 27 subjects with BC and the assumed true response rate of 50%, there is an 88% chance of observing at least 11 responses (in other words, the FNR is 12%). If the true response rate is only 25% rather than 50%, then there is a 5% chance that there will be at least 11 responses in 27 subjects (in other words, FPR is 5%). If 11 responses are observed (eg, 41% observed response rate), the lower limit of the 80% CI for the ORR is 28% (higher than historical ORR of 25%). The CI is calculated using Clopper-Pearson method.

For an expansion cohort of 37 subjects with cervical cancer and the assumed true response rate of 40%, there is an 87% chance of observing at least 12 responses (in other words, the FNR is 13%). If the true response rate is only 20% rather than 40%, then there is a 5% chance that there will be at least 12 responses in 37 subjects (in other words, FPR is 5%). If 12 responses are observed (eg, 32% observed response rate), the lower limit of the 80% CI for the ORR is 22% (higher than historical ORR of 20%). The CI is calculated using Clopper-Pearson method.

Table 8.1.2-1: Dose Expansion - Characteristics of the Simon 2-Stage Design[176]

Expansion Cohort	Historic ORR (%)	Target ORR (%)	Stage 1/ Total N	Stage 1 Responses Futility Boundary	FPR/1-FNR (%)	Probability of Early Stopping (%)
CRC, Ovarian Cancer	10	30	12/35	1	10/90	66
Bladder Cancer	25	50	10/27	2	10/90	53
Cervical Cancer	20	40	17/37	3	10/90	55
NSCLC, RCC	40	60	28/41	11	10/90	55

Abbreviations: CRC = colorectal cancer; FNR = false-negative rate; FPR = false-positive rate; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma.

The number of subjects receiving treatment for efficacy evaluation is approximate, and additional subjects may be treated in order to have sufficient response-evaluable subjects per expansion cohort.

8.1.3 Schedule and Dose Exploration and Safety Exploration

The purpose of Parts 4, 5, 6A, 7A, and 8 is to assess safety, tolerability, preliminary efficacy, PK, and PD information of BMS-986178 in combination with nivolumab administered with a less

frequent dosing schedule (q4w Part 4 and q12w Part 8 for BMS-986178) or BMS986178 in combination with higher dose of ipilimumab (Part 5) or BMS-986178 in combination with nivolumab and ipilimumab (Parts 6A and 7A). A minimum of 6 evaluable subjects will be treated in these parts at the MTD/RP2D chosen from Part 2A or Part 3A. Up to 12 subjects may be treated for further evaluation of safety, PK, or PD parameters.

Part 9

The purpose of Part 9 is primarily to evaluate safety and tolerability and secondarily to assess PD and investigate preliminary anti-tumor activityof BMS-986178 in combination with nivolumab and DPV-001 or DPV-001 in combination with nivolumab monotherapy. Part 9 includes a cohort for the combination of BMS-986178, nivolumab, DPV-001 vaccine, single dose cyclophosphamide (cohort 1) and a cohort for the combination of nivolumab, DPV-001 vaccine, and single dose cyclophosphamide (cohort 2). Subjects are to be randomized in a 2:1 ratio. A total of 12 subjects will be treated in cohort 1 and 6 evaluable subjects will be treated in cohort 2. Approximately 20% additional subjects may be enrolled in each cohort to ensure the number of evaluable subjects is achieved.

Assuming a 27% acceptable DLT rate, which corresponds to a Beta(1,2.7) distribution, Table 8.1.3-1 shows the risk associated with selecting a dose level as safe given the number of DLTs observed at that dose level based on the posterior probability associated with an observed DLT.

Table 8.1.3-1: Posterior Probability of DLT in Part 9 Assuming Observed DLTs

Number of Subjects DLT Evaluable in a Cohort	Number of Subjects with Observed DLT	Probability DLT Rate >33%	Probability DLT Rate >40%
6	1	16%	8%
	2	41%	25%
12	2	9%	3%
	3	23%	10%
18	3	5%	1%
	4	14%	4%
24	4	3%	1%
	6	17%	5%

Abbreviations: DLT=dose-limiting toxicities.

For all Parts that assess PD, administration of BMS-986178 in combination with nivolumab, nivolumab and ipilimumab, or nivolumab and DPV-001 in 6 to 12 subjects per dose and schedule level provides some precision of PD biomarker effect estimation. If more precise estimation is needed based on data observed, Part 9 may be further expanded to 24 subjects for Cohort 1 and 12 subjects for Cohort 2. To assess the PD effects, pre-treatment and on-treatment whole blood and serum samples and tumor biopsies will be required. It is of interest to ensure the precision of the

estimate of the ratio of on-treatment biomarker assessments to pre-treatment (baseline) levels. Assuming that a biomarker is measured as a continuous variable, a given number of subjects will provide the confidence that the estimate of the ratio of on-treatment to baseline values will be within 20% of the true value, as shown in Table 8.1.3-2.

Table 8.1.3-2: Probability that Estimated Ratio of On-treatment to Pre-treatment (Baseline) Value is Within 20% of True Value

Intra-subject Standard Deviation (Log-scale)		0.2	0.3	0.4	0.5	0.6	0.7	0.8
Probability	N = 6	92%	76%	62%	52%	44%	38%	34%
	N = 12	99%	90%	78%	68%	59%	52%	46%
	N = 24	100%	98%	92%	84%	76%	68%	62%

For example, for a biomarker (eg, activated and memory CD4 and CD8 T-cells) with an intrasubject standard deviation of 0.5, if the true ratio of post-baseline to baseline geometric means is 1.2 (increase from baseline is 20%), there is 68% probability that the estimated ratio would be within 0.96 and 1.44 (or a percent change between -4% and 44%) with 12 subjects per treatment arm and the probability is 84% with 24 subjects per arm. If the true increase from baseline is 60%, for a biomarker with the same variability, then there is 68% probability that the estimated percent change would be between 28% and 92% with 12 subjects per treatment arm and between 37% and 83% with 24 subjects per treatment arm.

Part 8

Up to approximately 20 evaluable subjects per dose cohort will be treated in Part 8. This sample size provides a 90% CI for the true proportion of subjects showing a change in receptor occupancy with width of 37% and 26% respectively when the observed proportion of subjects showing a change in receptor occupancy is 70% and 90%, as shown in Table 8.1.3-3. The maximum width of all 90% CIs is 40% and the maximum margin of error is 21% with a sample size of 20 per cohort.

Table 8.1.3-3: 90% Confidence Interval for the True Proportion of Subjects Showing a Biomarker Change

n	# subjects showing the trend	90% CI
20	14	(49%, 86%)
	18	(72%, 98%)

8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who signed an ICF and are registered into the IRT.
- All Treated Subjects: All subjects who received at least 1 dose of study medication.

- The PK data set includes all available concentration-time data from subjects who received any BMS-986178, nivolumab, or ipilimumab.
- The immunogenicity data set consists of all available immunogenicity data from subjects who received BMS-986178, nivolumab, or ipilimumab.
- The biomarker data set includes all available biomarker data from subjects who received any study drug(s).
- Response-evaluable subjects: All treated subjects with measurable disease and any of the following: 1) at least 1 post-baseline tumor measurement, 2) clinical progression, or 3) death.

Analyses of safety, extent of exposure, biomarkers, PK, preliminary efficacy, immunogenicity, and PD will be based on all treated subjects.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The assessment of safety will be based on the incidence of AEs, SAEs, AEs leading to discontinuation, and deaths. In addition, clinical laboratory test abnormalities will be examined.

AEs and laboratory values will be graded according to NCI CTCAE v4.03.

8.3.2 Secondary Endpoint(s)

8.3.2.1 Efficacy

The anti-tumor activity of BMS-986178 alone, in combination with nivolumab and/or ipilimumab, or in combination with nivolumab and DPV-001 and nivolumab in combination with DPV-001 will be measured by ORR based on RECIST v1.1. The above will be determined based on tumor measurements occurring at baseline, every 8 weeks (±1 week) for Parts 1-7 and 9 or every 12 weeks (±1 week) for Part 8 during the treatment period.

- Best overall response (BOR) is assessed by investigator and/or BICR per RECIST 1.1 criteria.
- ORR is defined as the proportion of all treated subjects whose BOR is either CR or PR.

8.3.2.2 Pharmacokinetics

Selected BMS-986178 parameters, such as Cmax, Tmax, AUC(0-t), and AUC(TAU), will be assessed in 2 cycles depending on the schedule for monotherapy or in combination with nivolumab and/or ipilimumab. Parameters such as Ctau, CLT, Css-avg, accumulation index (AI), and effective elimination half-life (T-HALFeff) will be assessed in the second cycle when intensive PK are collected. A separate listing, summary, and plot will be generated for Ctrough.

8.3.2.3 Immunogenicity

The secondary objective of immunogenicity will be assessed by the frequency of positive ADA to BMS-986178 or nivolumab or ipilimumab.

8.3.2.4 Pharmacodynamics

The secondary objective of pharmacodynamics will be assessed by the proportion of subjects showing a change in pharmacodynamic biomarkers such as soluble OX40 and peripheral OX40 receptor occupancy along with tumor pharmacodynamic of BMS-986178 in combination with nivolumab or nivolumab monotherapy (Part 8). and sustained T cell expansion with DPV-001 in combination with nivolumab or nivolumab monotherapy (Part 9)

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated. Summary statistics for age, body weight, and height will be tabulated.

8.4.2 Efficacy Analyses

The efficacy analyses will be performed on all treated subjects. Efficacy analyses based on response-evaluable subjects may be performed for interim analyses when the minimum follow-up period is less than sufficient to warrant adequate interpretation of results. Listing of tumor measurements will be provided by subject and study day in each arm and dose level. Individual subject's BOR will be listed based on RECIST 1.1.

To describe the anti-tumor activity of BMS-986178 alone, in combination with nivolumab and/or ipilimumab, or in combination with nivolumab and DPV-001 and nivolumab in combination with DPV-001, ORR will be calculated. ORR and corresponding two-sided exact 95% CI by the Clopper-Pearson method will be provided by treatment and/or dose level and tumor type.

8.4.3 Safety Analyses

All recorded AEs will be listed and tabulated by system organ class, preferred term, and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator, and abnormalities, if present, will be listed

8.4.4 Pharmacokinetic Analyses

All individual PK parameters will be listed for each analyte, including any exclusions and reasons for exclusion from summaries. Summary statistics will be tabulated for each BMS-986178 PK parameter by treatment. Geometric means and coefficients of variation will be presented for Cmax, AUC(0-t), AUC(TAU), Ctau, CLT, Css-avg, and AI. Medians and ranges will be presented for

Tmax. Medians and ranges will be presented for Tmax. Means and standard deviations will be presented for all other PK parameters (eg, T-HALFeff).

BMS-986178 dose dependency will be assessed in dose escalation monotherapy. To describe the dependency on dose of BMS-986178, scatter plots of Cmax, AUC(0-t), and AUC(TAU) versus dose may be provided at the cycles when these PK parameters are assessed, as specified in Section 5.5. Exploratory assessments of dose proportionality based on a power model with CI around the power coefficient may be performed. Nivolumab and ipilimumab EOI and trough (Ctrough) concentrations and BMS-986178 trough concentration will be tabulated by treatment and study day using summary statistics. These data may also be pooled with other datasets for population PK analysis, which will be presented in a separate report.

8.4.5 Biomarker Analyses

In Part 9, summary statistics for the proportion of subjects showing a change in pharmacodynamics biomarkers will be tabulated by treatment cohort.

[redacted]

8.4.7 Outcomes Research Analyses

Not applicable.

8.4.8 Other Analyses

A listing of all available immunogenicity data will be provided by treatment, dose, and immunogenicity status. The frequency of subjects with positive ADA assessment of BMS-986178, nivolumab, or ipilimumab will be summarized.

8.5 Interim Analyses

Administrative interim analysis for internal decision making or external publication purpose may be performed. No formal inferences requiring any adjustment to statistical significance level will be performed.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable

opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to BMS.

9.1.2.1 Source Documentation

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures.

Such systems may include, but are not limited to, electronic medical/health records, AE tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

BMS will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study and BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product. Records or logs must comply with applicable regulations and guidelines and should include:

- Amount received and placed in storage area
- Amount currently in storage area
- Label identification number or batch number
- Amount dispensed to and returned by each subject, including unique subject identifiers
- Amount transferred to another area/site for dispensing or storage
- Nonstudy disposition (eg, lost, wasted)
- Amount destroyed at study site, if applicable
- Amount returned to BMS
- Retained samples for bioavailability/bioequivalence, if applicable
- Dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents, or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS EDC tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the or electronic SAE form and Pregnancy Surveillance form, respectively. If an electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS EDC tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS EDC tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and

must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.
Additional Research	Those scientific activities which cannot be reasonably anticipated at the time of trial design, for which samples from study subjects may be collected and/or retained. Examples of additional research include, but are not limited to, new assay development and validation, companion diagnostic development, new hypotheses in the interaction of drug and the human body, and exploration of emerging science in the understanding of disease.

11 LIST OF ABBREVIATIONS

Term	Definition
5-FU	5-fluorouracil
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AFP	alpha fetal protein
AI	accumulation index
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APC	antigen-presenting cell
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-t)	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in 1 dosing interval
BC	bladder cancer
BCR	B-cell receptor
BICR	Blinded Independent Central Review
BLA	Biologics License Application
BLRM	Bayesian Logistic Regression Method
BMS	Bristol-Myers Squibb
BOR	best overall response
BSC	best supportive care
BUN	blood urea nitrogen
C12	concentration at 12 hours

Term	Definition
C	Cycle
CAP	College of American Pathologists
Cavgss	steady-state time-averaged concentration
CBC	complete blood count
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
cHL	classical Hodgkin lymphoma
CI	confidence interval
CL	clearance
CLss	steady-state clearance
CLT	total body clearance
Cmax	maximum observed concentration
Cmaxss	steady-state peak concentration
CMI	cell-mediated immunity
Cminss	steady-state trough concentration
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CrCL	creatinine clearance
CRF	case report form, paper or electronic
CRP	C-reactive protein
Css-avg	average concentration over a dosing interval (AUC[TAU]/tau)
CT	computed tomography
CTA	clinical trial agreement
Ctau	the observed concentration at the end of a dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte associated antigen-4
Ctrough	Trough observed plasma concentration
CV%	Percent coefficient of variation
D	day

Term	Definition
DRiPs	defective ribosomal products
CV	coefficient of variation
DEHP	diethylhexyl phthalate
DLT	dose-limiting toxicity
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOI	end of infusion
EOT	end of treatment
ER	estrogen receptor
EWOC	escalation with overdose control
Fc	fragment crystallizable
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed, paraffin-embedded
FIH	first-in-human
FISH	fluorescence in situ hybridization
FNR	false-negative rate
FPR	false-positive rate
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
Geo Mean	geometric mean
GGT	gamma-glutamyl transferase
gMDSC	granulocytic myeloid-derived suppressor cell
GITR	glucocorticoid-induced TNFR-related gene
HCC	hepatocellular carcinoma

Term	Definition
hCG	human chorionic gonadotrophin
HER2	human epidermal growth factor receptor 2
hERG	human Ether-à-go-go-Related Gene (hERG)
HIV	human immunodeficiency virus
HPV	human papillomavirus
HR	hazard ratio
HRT	hormone replacement therapy
IASLC	International Association for the Study of Lung Cancer
IB	Investigator Brochure
ICD	International Classification of Diseases
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	intradermal
IEC	Independent Ethics Committee
IFN-γ	interferon-γ
IgG1	immunoglobulin G1
IgG2	immunoglobulin G2
IHC	immunohistochemistry
IMDC	International Metastatic RCC Database Consortium
IMP	investigational medicinal products
IL	interleukin
IN	intranodal
IO	immuno-oncology
IP	intraperitoneal
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	Interactive Response Technology
IUD	intrauterine device
IV	intravenous
KPS	Karnofsky Performance Scale

Term	Definition
LDH	lactic acid dehydrogenase
LFT	liver function test
mAb	monoclonal antibody
MABEL	minimal anticipated biologic effect level
mCRC	metastatic colorectal cancer
MC38	murine colon carcinoma cell line 38
MDSC	myeloid-derived suppressor cell
MHC	major histocompatibility
mOS	median overall survival
mPFS	median progression free survival
mRCC	metastatic renal cell carcinoma
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSKCC	Memorial Sloan-Kettering Cancer Center
MST	Medical Surveillance Team
MTD	maximum tolerated dose
N	number of subjects or observations
NCA	non-compartmental analysis
NCI	National Cancer Institute
NK	natural killer
NKT	natural killer T
NSCLC	non-small cell lung cancer
OC	ovarian cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PBT	platinum-based therapy
PCR	polymerase chain reaction
PD	pharmacodynamics

Term	Definition
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand-1
pDILI	potential drug-induced liver injury
PET	positron emission tomography
PFS	progression free survival
PFSR	progression free survival rate
PgR	progesterone receptor
PK	pharmacokinetics
PR	partial response
PSA	prostate-specific antigen
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
q6w	every 6 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RO	receptor occupancy
RP2D	recommended Phase 2 dose (s)
RT-PCR	reverse transcriptase polymerase chain reaction
RT-qPCR	real-time quantitative polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SLiPs	short-lived proteins
SNP	single-nucleotide polymorphism
SOC	standard of care
T	time
T3	triiodothyronine

Term	Definition
T4	thyroxine
TCGA	The Cancer Genome Atlas
TCR	T-cell receptor
TF	tumor free
TGI	tumor growth inhibition
TIL	tumor-infiltrating lymphocyte
T-HALF	half life
T-HALFeff	effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure (exposure measure includes AUC[TAU], Cmax and Ctau)
Tmax	time of maximum observed concentration
TNBC	triple negative breast cancer
TNF-α	tumor necrosis factor-α
TNFRsf	tumor necrosis factor receptor super family
Treg	regulatory T-cell
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
Vc	volume of central
VEGF	vascular endothelial growth factor
VS	vital signs
Vss	volume of distribution at steady state
Vz	volume of distribution of terminal phase (if IV and if multi-exponential decline)
WOCBP	women of childbearing potential

APPENDIX 3 RECIST 1.1

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least 1 measurable tumor lesion. When computed tomographic (CT) scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

Central assessments may be planned for this study. Copies of all scans should be kept at the site as part of the subject study file. At the Sponsor's discretion, scans may be collected centrally for further analysis.
At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1 Measurable Lesions

Measurable lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT/magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- *Malignant lymph nodes*: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥ 15 mm in the ***short*** axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow-up, only the ***short*** axis will be measured and followed.

1.2 Non-Measurable Lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions
- Lesions considered truly non-measurable include the following: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of the skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by reproducible imaging techniques

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone Lesions

- Bone scan, positron emission tomography (PET) scan or plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components* that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.3.2 Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

1.3.3 Lesions with Prior Local Treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

1.4 Specifications by Methods of Measurements

1.4.1 Measurement of Lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 30 days before the beginning of the treatment.

1.4.2 Method of Assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

1.4.2.1 CT/MRI Scan

CT/MRI is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT/MRI scan is based on the assumption that CT/MRI slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

1.4.2.2 Chest X-ray

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

1.4.2.3 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

1.4.2.4 Ultrasound

Ultrasound is ***not*** useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

1.4.2.5 Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is ***not*** advised.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

2.1 Target Lesions

When more than 1 measurable lesion is present at baseline all lesions up to **a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as *target lesions*** and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their **size** (lesions with the longest diameter), should be representative of all involved organs, and should lend themselves to ***reproducible repeated measurements***.

A ***sum of the diameters*** (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the ***baseline sum diameters***. If lymph nodes are to be included in the sum, then as noted below, only the ***short*** axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

2.1.1 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

2.2 Non-Target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as **'present'**, **'absent'**, or in rare cases **'unequivocal**

progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION

3.1 Evaluation of Target Lesions

Complete Response (CR): **Disappearance of all target lesions.** Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a **30% decrease in the sum of diameters of target lesions**, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a **20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study*** (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an **absolute increase of at least 5 mm**. (*Note:* The appearance of 1 or more new lesions is also considered progression.)

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

3.1.1.2 Target Lesions That Become 'Too Small to Measure'

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5-mm CT slice thickness (but should not be changed with varying CT slice thickness).

3.1.1.3 Target Lesions That Split or Coalesce on Treatment

- When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.
- As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

3.2 Evaluation of Non-Target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) above the normal limits.

Progressive Disease (PD): *Unequivocal progression* of existing non-target lesions. (*Note:* The appearance of 1 or more new lesions is also considered progression.)

3.2.1 Special Notes on Assessment of Non-Target Lesions

The concept of progression of non-target disease requires additional explanation as follows:

3.2.1.1 When the Subject Also Has Measurable Disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

3.2.1.2 When the Subject Has Only Non-Measurable Disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable), a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: that is, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large'

or an increase in lymphangitic disease from localized to widespread or may be described in protocols as 'sufficient to require a change in therapy'.

- If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point.

3.2.1.3 Tumor Markers

Tumor markers *alone* cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a subject to be considered as having attained a complete response.

3.3 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: that is, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (eg, some 'new' bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered that reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. *If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.*

3.3.1 FDG-PET Evaluation

While [^{18}F] fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of the qualitative assessment of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial positive FDG-PET scan).

– If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

4 RESPONSE CRITERIA

4.1 Timepoint Response

A response assessment should occur at each timepoint specified in the protocol.

For subjects who have **measurable disease** at baseline Table 4.1-1 provides a summary of the overall response status calculation at each timepoint.

Table 4.1-1: Timepoint Response: Subjects with Target (+/– Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE =not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the subject is **not evaluable (NE)** at that timepoint. If only a subset of lesion measurements are made at an assessment, the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned timepoint response.

4.1.1 Confirmation Scans

- **Verification of Response:** *Confirmation of PR and CR is required after at least 4 weeks following initial assessment to ensure responses identified are not the result of measurement error.*

4.2 Best Overall Response: All Timepoints

The *best overall response* is determined once all the data for the subject are known. It is the best response recorded from the start of the study treatment until the date of objectively documented progression based on RECIST v1.1, taking into account any requirement for confirmation, or the date of subsequent anti-cancer therapy, whichever occurs first in the study. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Best response is defined as the best response across all timepoints with subsequent confirmation. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent timepoint as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 4.2-1. When SD is believed to be best response, it must meet the protocol specified minimum time from baseline. Measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6 to 8 weeks) that is defined in the study protocol.

Table 4.2-1: Best Overall Response When Confirmation of CR and PR Is Required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR

Table 4.2-1: Best Overall Response When Confirmation of CR and PR Is Required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall Response
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since the disease must have reappeared after CR). The best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.3 Duration of Response

4.3.1 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.3.2 Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

APPENDIX 4 ECOG PERFORMANCE STATUS

ECOG Performance Status[a]	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities Up and about more than 50% of waking hours
3	Capable of only limited self-care Confined to bed or chair more than 50% of waking hours
4	Completely disabled Cannot carry on any self-care Totally confined to bed or chair
5	Dead

[redacted]

APPENDIX 5 INTERNATIONAL METASTATIC RCC DATABASE CONSORTIUM (IMDC) PROGNOSTIC CRITERIA

Adverse Prognostic Factors
Clinical
KPS < 80% Time from diagnosis to treatment < 1 year
Laboratory
Hemoglobin < LLN Corrected calcium > ULN Absolute neutrophil count > ULN Platelet count > ULN

LLN = Lower limit of normal
ULN = Upper limit of normal

Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 (4.0 - serum albumin [g/dL]), where 4.0 represents the average albumin level in g/dL.

Corrected calcium (mmol/L) = measured total Ca (mmol/L) + 0.02 (40 - serum albumin [g/L]), where 40 represents the average albumin level in g/L

Risk Group Based on Number of Adverse Prognostic Factors	
Number of Adverse Prognostic Factors Present	**Risk Group**
0	Favorable
1-2	Intermediate
3-6	Poor

[redacted]